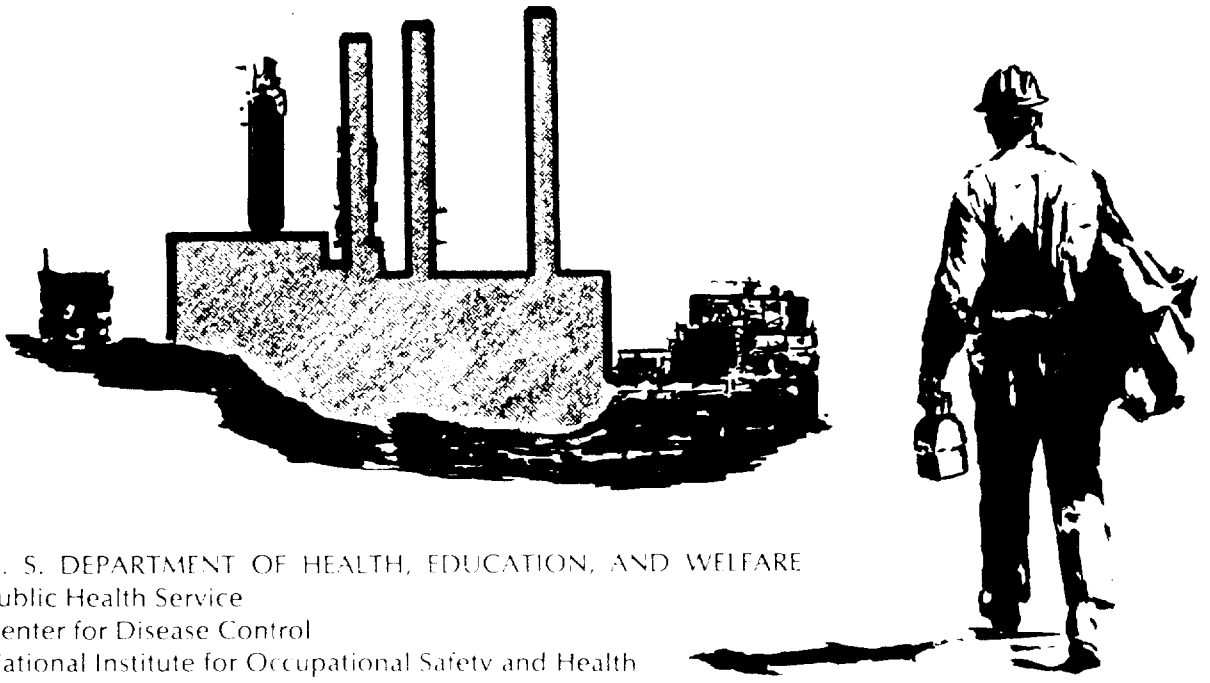
NIOSH

CRITERIA FOR A RECOMMENDED STANDARD....

OCCUPATIONAL EXPOSURE DURING THE MANUFACTURE AND FORMULATION OF PESTICIDES



U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
Center for Disease Control
National Institute for Occupational Safety and Health

criteria for a recommended standard....

OCCUPATIONAL EXPOSURE DURING THE MANUFACTURE AND FORMULATION OF PESTICIDES

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
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PREFACE

The Occupational Safety and Health Act of 1970 emphasizes the need for standards to protect the health and provide for the safety of workers occupationally exposed to an ever-increasing number of potential hazards. The National Institute for Occupational Safety and Health (NIOSH) has implemented a formal system of research, with priorities determined on the basis of specified indices, to provide relevant data from which valid criteria for effective standards can be derived. Recommended standards for occupational exposure, which are the result of this work, are based on the effects of exposure on health. The Secretary of Labor will weigh these recommendations along with other considerations, such as feasibility and means of implementation, in developing regulatory standards.

Successive reports will be presented as research and epidemiologic studies are completed and as sampling and analytical methods are developed. Criteria and standards will be reviewed periodically to ensure continuing protection of workers.

The contributions to this document on pesticide manufacturing and formulating industries by NIOSH staff members, the review consultants, the reviewer selected by the American Conference of Governmental Industrial Hygienists (ACGIH), other Federal agencies, and by Robert B. O'Connor, M.D., NICSH consultant in occupational medicine, are gratefully acknowledged.

The views expressed and conclusions reached in this document, together with the recommendations for a standard, are those of NIOSH. They are not necessarily those of the consultants, the reviewer selected by the ACGIH, or other Federal agencies that evaluated the document. The comments from the review consultants and other reviewers have been considered carefully and, together with the criteria document, have been sent to the Occupational Safety and Health Administration for consideration in setting occupational safety and health standards. The review consultants, Federal agencies, and professional society to which this document was submitted are listed on pages vi, vii, and viii.

J. Michael Lane, M.D.
Acting Director, National Institute
for Occupational Safety and Health

The Division of Criteria Documentation and Standards Development, National Institute for Occupational Safety and Health, had primary responsibility for the development of the criteria and recommended standard for pesticides. Jimmy L. Perkins of this Division served as criteria manager. JRB Associates, Inc., developed the basic information for consideration by NIOSH staff and consultants under contract No. 210-77-0006.

The Division review of this document was provided by Jon R. May, Ph.D. (Chairman), J. Henry Wills, Ph.D., Charles C. Hassett, Ph.D., Clara H. Williams, Ph.D., David Brown and A. Blair Smith, M.D. (Division of Surveillance, Hazard Evaluations, and Field Studies), and James Gideon (Division of Physical Sciences and Engineering).

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- Office of Pesticide Programs

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I. RECOMMENDATIONS FOR A STANDARD FOR PESTICIDE MANUFACTURING AND FORMULATING INDUSTRIES

The National Institute for Occupational Safety and Health (NIOSH) recommends that employee exposure to pesticides in manufacturing and formulating workplaces be controlled by adherence to the following sections. The recommended standard is designed to protect the health and safety of employees in pesticide manufacturing and formulating facilities over their working lifetime. Compliance with all sections of the recommendations will establish an increased level of control over the workplace environment of pesticide manufacturers and formulators and should thus prevent or greatly reduce adverse effects of pesticides on the health and safety of employees. Sufficient technology exists to permit compliance with the recommended standard. The criteria and standard will be subject to review and revision, as necessary.

Environmental (workplace air) limits are not included in the recommended standard. Such values have been promulgated for many pesticides by The Occupational Safety and Health Administration (OSHA), and NIOSH has previously recommended such limits individually for various pesticides (see Appendices III and IV). NIOSH recommends compliance with promulgated environmental limits and adoption of new environmental limits in those cases where the NIOSH recommended environmental limits

differ from those already promulgated. These include the limits recommended for substances such as parathion, methyl parathion, creosote, ethylene dibromide, and dinitro-o-cresol. In this document, emphasis has been placed on work practices, engineering controls, and medical surveillance programs to protect workers from the adverse effects of pesticide exposure in manufacturing and formulating operations. A number of factors led NIOSH to this decision. First, workers in pesticide manufacturing and formulating operations are exposed to a large number of different chemicals and substances. Sampling and analytical methods to determine airborne exposure levels for each substance would need to be highly sophisticated. Second, exposure via other routes, especially dermal, has proven to be of critical importance for many pesticides. The relationship between dermal exposure hazards and airborne levels is scientifically tenuous, and adherence to environmental (workplace air) limits does not always protect the employee from significant dermal exposure. Third, NIOSH believes that immediate action is needed to protect workers in pesticide manufacturing and formulating plants. The time required to evaluate all the documented toxic effects and to establish scientifically valid environmental (workplace air) limits for approximately 1,500 pesticides would be a matter of years. Consequently, reliance on engineering controls, work practices, medical examinations, and education of employers and employees is seen as the first step in attempting to prevent additional poisoning episodes similar to those involving Kepone and leptophos.

Because of the wide range of adverse health effects that can arise from employee exposure in manufacturing and formulating facilities, it was determined that a single set of work practices and engineering controls would not effectively protect health and safety and at the same time avoid placing unnecessary burdens on both employees and employers in such facilities. Therefore, various classification schemes used by organizations in the US and in other countries were examined for the purpose of grouping pesticides according to toxicity. A considerable degree of similarity was found among such schemes.

Given the similarity that exists among the various schemes examined and the absence of significant differences in scientific merit, the system used by the US Environmental Protection Agency (EPA) was selected as the basis for the approach recommended in this document.

These criteria for a pesticide standard apply only to occupations in pesticide manufacturing and formulating. This includes manufacturing, formulating, packaging, mixing, blending, or repackaging of any pesticide active ingredient. Occupational exposure is defined as contact with any pesticide or other chemical during the manufacture and formulation of pesticides. "Pesticide" is used herein as the generic term meaning any substance or mixture of substances intended for those uses described by definition in the Federal Environmental Pesticide Control Act (FEPCA): preventing, destroying, repelling, or mitigating any pest and regulating, defoliating, or desiccating any plant (40 CFR 162). All pesticide active ingredients

registered with the EPA are covered by this recommended standard. Other chemicals to which workers are potentially exposed in pesticide manufacturing and formulating operations (such as intermediates, impurities, diluents, emulsifiers, carriers, inerts, and propellants) are also covered by the provisions contained herein, as well as by provisions in any separate standards applicable for such chemicals, eg, xylene. In the case of conflicts between this recommended standard and any existing standard, NIOSH recommends that the more stringent standard apply.

The standard was not designed for the population-at-large, or for users of pesticides who are already regulated by other agencies such as the US Department of Transportation (DOT), EPA, and the Food and Drug Administration (FDA). Application of this recommended standard to situations other than the occupational settings specified above is not warranted.

Each section of the recommended standard contains three sets of requirements that pertain to the three groups of pesticides listed in Appendix I. Pesticides in Group III are the least toxic and therefore require the least stringent level of control. Group II pesticides produce acute effects at lower dose levels than Group III pesticides; controls for Group II include all of the Group III controls with some additional, more stringent requirements. Pesticides in Group I produce acute effects at extremely low-dose levels or serious irreversible effects; therefore, pesticides in Group I require those controls for Groups III and II and additional requirements where noted.

Classification by acute toxicity is based on oral and dermal LD50's and inhalational LC50's in mammals, and includes both systemic and local effects. Certain pesticides have been classified based on irreversible effects, including probable and potential carcinogenicity, and potential teratogenicity, mutagenicity, neurotoxicity, and reproductive effects, as demonstrated in animal test systems and human epidemiologic studies. Insecticides which inhibit cholinesterase (ChE) activity are also noted. Numeric definitions of the three pesticide groups are presented in Table VI-1. By necessity, only selected portions of the published literature on chronic adverse health effects of this extremely large and diverse group of chemicals were reviewed and evaluated in this document. As new data regarding toxicity and potential hazards are developed and evaluated, it is highly probable that pesticide classifications will change over time.

It should be emphasized that pesticides are an extremely diverse group of substances. There is a potential for a wide variety of toxic effects throughout the group. For many pesticides, the possibility of dermal exposure and subsequent absorption presents a greater problem to workers than does exposure through inhalation. In addition, many establishments by their nature manufacture or formulate a vast number of pesticides with varying toxicities; the possible synergisms of these combinations of substances are unknown. Consequently, there is a need for constant surveillance and monitoring and thorough recordkeeping to make sure that employees are following proper

procedures so that their health is not compromised.

Section 1 - Medical

GROUPS III, II, AND I

(a) Preplacement or initial medical examinations shall be made available as described below for all employees subject to exposure to pesticides:

(1) Comprehensive medical and work histories with emphasis directed toward the hepatic, renal, and central nervous systems and toward evidence of glaucoma, cardiovascular, or respiratory disease. The use of drugs or any illnesses resulting from past exposures to pesticides should also be noted.

(2) Comprehensive physical examination giving particular attention to the eyes, liver, kidneys, lungs, and the central and peripheral nervous systems.

(3) After a review of the type and amount of exposure, clinical tests such as pulmonary function, chest X-ray, liver enzyme determinations, and urinalysis may be carried out at the discretion of the responsible physician.

(4) A judgment of the worker's ability to use negative and positive pressure respirators.

(5) Red blood cell (RBC) ChE activity shall be measured for determination of a preexposure baseline if the employee will potentially be exposed, or for determination of a working baseline if the employee has previously been and will continue to be exposed to those pesticides indicated as ChE inhibitors in Appendix I.

"Preexposure baseline" for RBC ChE is defined as the mean of two ChE activity determinations, each of which is derived from a separate sample of blood taken at least 1 day apart after a period of at least 60 days without known exposure to any ChE-inhibiting compounds. If the determinations produce values differing by more than 15%, additional determinations on new samples must be performed until successive tests do not differ by more than 15%.

"Working baseline" for ChE is defined as the mean of two ChE activity determinations, each of which is derived from a separate sample of blood taken at least 1 day apart and differing by no more than 15%, or the arithmetic mean of normal values for an appropriate control population of adults for that laboratory, whichever is higher. A "working baseline" is determined only for an individual whose work history does not permit a preexposure baseline to be determined as specified in this section.

"Mean of normal values" is defined as the arithmetic mean of ChE activities for healthy adults as determined by the laboratory's experience with repeated analyses, but which is not inconsistent with the mean baseline activities presented in Appendix II. Working, or preexposure, baseline RBC ChE activities shall be determined within 60 days of promulgation of a standard based on this recommendation.

(b) Periodic examinations shall be made available on at least an annual basis and shall include at least:

(1) Interim medical and work histories.

(2) Physical examination as outlined in (a)(2)

and (3), above.

(c) Periodic measurement of RBC ChE activity shall be made available for workers exposed to organophosphorus (OP) insecticides as follows:

(1) Subsequent to the determination of a preexposure or working baseline, each employee occupationally exposed to OP insecticides, indicated in Appendix I as being ChE inhibitors, shall have his ChE activity determined at 1-week intervals. These intervals may be initially reduced to testing as frequently as every day, or may be increased after three weekly determinations to testing as frequently as every 8 weeks, based on the decision of the responsible physician after consideration of the following for each employee:

(A) The toxicity of the pesticides to which the employee may be exposed.

(B) The potential duration and concentration of the pesticide exposure.

(C) The state of health of the employee.

(D) The results of previous ChE determinations.

(2) Unacceptable exposure to OP insecticides indicated in Appendix I as ChE inhibitors is demonstrated when the activity of RBC ChE is decreased to below 70% of baseline. The employee shall be advised of such a finding, and an industrial hygiene survey shall be conducted in the workplace of the affected employee unless the cause of the exposure is known and corrective action has been initiated. This survey shall

include an assessment of the dermal exposure potential. Based on the results of this survey, necessary corrective action shall be accomplished.

In addition, an employee whose RBC ChE activity is decreased to below 60% of the employee's baseline level shall be removed from potential exposure and placed under medical observation.

(3) An employee who has been removed from pesticide exposure shall not be allowed to return to work involving occupational pesticide exposure until his RBC ChE activity has returned to at least 75% of the working or preexposure baseline values or unless the responsible physician has approved his return.

(4) Each employee shall be given a copy of the results of his initial and periodic tests, and of any special ChE test results as soon as possible after the test, and an interpretation thereof.

(5) Procedures for collection and analysis of blood samples for ChE activity determinations shall be as provided in Appendix II or by any method shown to be at least equivalent in accuracy, precision, and sensitivity to that specified.

(d) Emergency first-aid services shall be established, under the direction of the responsible physician, to provide care to any worker acutely intoxicated by pesticides.

(e) Appropriate medical services and surveillance shall be provided to any worker with adverse health effects reasonably

assumed or shown to be due to occupational exposure to pesticides.

(f) During examinations, applicants or employees found to have medical conditions such as skin disease, chronic lung disease, glaucoma, or abnormalities of the central or peripheral nervous systems that could be directly or indirectly aggravated by exposure to pesticides shall be counseled as to the possible increased risk of impairment of their health from working with the substances. Employees should be further counseled about reproductive effects that have been noted in male workers and in laboratory animals involving certain pesticides. The significance to humans of the effects in laboratory animals are not fully known, but they do indicate that exposure should be minimized, particularly in women of child-bearing age. In addition, residues of some organochlorine (OC) and carbamate pesticides have been found in human breast milk. Therefore, women who may bear or nurse children should avoid any contact with these materials.

(g) A complete examination including all aspects of paragraph (a) shall be offered to all employees within 1 month after employment ends.

(h) The employer shall provide the consulting physician for each pesticide operation with information on the following items:

(1) Plant layout and operations.

(2) Hazardous substances used by workers.

(3) Physical, chemical, and toxicologic

properties of hazardous substances used by workers.

(4) Symptoms of intoxication by hazardous substances.

(5) Treatment for accidental exposures to hazardous substances.

Section 2 - Labeling and Posting

GROUP III

(a) All containers of pesticides to be used within pesticide manufacturing or formulating facilities shall be labeled.

(1) Labels shall include the following information:

(A) Contents, by chemical and common names.

(B) Fire hazard.

(C) Toxicity hazard.

(D) Storage and handling precautions.

(E) First aid for inhalation, ingestion, and contact with skin or eyes.

(2) The information shall be arranged as in the following example:

PESTICIDE X

Chemical Name

MAY BE FATAL IF INHALED, ABSORBED THROUGH SKIN,

OR INGESTED. EXPLOSION MAY RESULT FROM HEAT OR SHOCK.

Store in cool place.
Protect from sunlight.
Avoid contact with skin and eyes.
Use only with adequate ventilation.

First Aid: In case of eye or skin contact wash immediately. If clothes become contaminated, remove at once, wash body with soap and water, and call physician without delay. Pesticide X is a ChE inhibitor.

(b) All entrances to areas where pesticides are manufactured, formulated, repackaged, stored, or otherwise handled shall be posted with signs specifying:

(1) Special clothing and personal protective equipment necessary for entry.

(c) All emergency-use personal protective clothing and equipment shall be clearly labeled as to limitations in its use.

(d) All warning signs shall be printed both in English and in the predominant language of non-English-reading workers. Workers unable to read labels and signs provided shall receive information regarding hazardous areas and shall be informed of the instructions printed on labels and signs.

GROUP II

Group III Labeling and Posting requirements apply, with the following additions:

(b) (2) Hazardous materials which may be encountered.

(b) (3) Restrictions on personnel who may enter and on activities (such as eating) which may be performed therein.

(e) All pesticide-processing equipment and pipes shall be properly identified by such means as labeling or color coding to indicate that pesticides are contained therein.

(f) All nondisposable routinely used personal protective equipment shall be labeled as to assignee.

(g) All working areas, lavatories, toilet rooms, shower rooms, locker rooms, eating areas, and smoking areas shall be posted to remind employees of applicable parts of Section 6.

GROUP I

Group II Labeling and Posting requirements apply with the following additions and changes:

(a) (1) (C) Toxicity hazard, including an indication of any probable or suspect carcinogenic, mutagenic, teratogenic, neurotoxic, or reproductive health effect.

(b) (4) A warning that the area is restricted.

(e) All pesticide-processing equipment shall be labeled by color code or other means to identify hazardous contents and any extremes in temperature or pressure.

Section 3 - Personal Protective Clothing and Equipment

(a) Work Clothing

GROUP III

Employers shall provide a means for storing contaminated work clothing in a location separate from street clothing to prevent contamination of street clothing.

GROUPS II AND I

(1) All employees working in potential exposure areas shall be required to wear the following set of work clothing:

(A) Washable socks and underwear.

(B) Washable or disposable coveralls or pants and long-sleeved shirts, aprons, or other special outerwear.

(C) Washable work footwear or disposable footwear covers.

(D) Washable cap, if a hard hat is not required.

(2) Employees shall be required to wear a clean set of work clothing each day. A complete second set of clean work clothing shall be provided and used to replace any that becomes obviously contaminated during the workshift.

(3) Employers shall provide a means for storing contaminated work clothing from the time it is removed by employees until its disposal or laundering. Such means shall:

(A) Clearly identify the nature of contamination.

(B) Prevent the contamination from being disseminated.

(4) Employers shall also provide a means for the disposal or laundering of all contaminated garments. All persons engaged in laundering such garments shall be instructed as to the pesticide hazard. For garments worn while handling carbamates or

OP's, laundering shall include presoaking in an alkaline solution (preferably of pH 10 or greater), washing, and subsequent rinsing. Garments laundered by other than the employer shall be reused only by the employer.

(b) Personal Protective Equipment

GROUP III

(1) Employees who may be exposed to pesticides in a dust or powdered form shall wear, in addition to their set of work clothing:

(A) Washable gloves.

(2) Employees who may be exposed to pesticides in a liquid or in a wet or hygroscopic solid form shall wear, in addition to their set of work clothing, the following:

(A) Chemical goggles, and where chemical burns are a hazard, a face shield.

(B) Gloves made of minimally permeable material.

(C) Footwear or footwear covers made of minimally permeable material.

(D) An apron or similar body covering made of minimally permeable material to prevent contamination of clothing.

(E) A type of hat whose configuration prevents spilled liquids from dripping on the neck or into the face of the wearer.

(3) All personal protective equipment shall be

inspected at least quarterly by the employer to check for contamination, deterioration, or loss of function and shall be replaced if necessary.

GROUP II

Group III requirements for Personal Protective Equipment apply with the following additions and change:

(3) Inspection frequency shall be at least monthly.

(4) Personal protective equipment shall be cleaned or replaced each time it is used. Extra issues of clean protective equipment shall be provided and used to replace any which becomes obviously contaminated during the workshift.

(5) Employers shall make appropriate provisions for the washing of personal protective equipment, including:

(A) Sink with running water.

(B) Decontamination solution to remove or neutralize pesticides.

(C) Disinfectant or sanitizing rinse.

(D) Drying rack or disposable towels.

GROUP I

Group II requirements for Personal Protective Equipment apply with the following changes:

(3) Inspection frequency shall be at least weekly.

(5) Employers shall be responsible for decontamination, sterilization, and maintenance of protective equipment.

(c) Respiratory Protection

GROUPS III AND II

(1) Protection of employees from exposure to airborne pesticides may not be achieved by the use of respirators except:

(A) During the development, installation, testing, maintenance, or repair of required engineering controls.

(B) For conducting operations such as maintenance, repair, or cleanup of spills.

(C) During emergencies.

(2) Employers shall use the survey data required in Section 8(a)(1) to determine which locations and employees shall be provided with emergency-use respirators.

(3) Respirators shall be those approved by NIOSH and the Mine Safety and Health Administration (MSHA) as specified under 30 CFR 11.

(4) Employers shall prepare written procedures for use of respirators. The procedures for each type of respirator shall include, but not be limited to, the following:

(A) By whom and where the respirator is to be worn.

(B) Limits as to materials and concentrations against which the respirator affords protection.

(C) Manner in which the respirator is to be put on, worn, and taken off.

(D) Frequency of servicing, disinfecting,

cleaning, inspecting, and replacing parts of the respirator.

(E) Manner and location of respirator storage.

(5) Employers shall maintain a written log for all nondisposable respirators which includes:

(A) Date of purchase; shelf-life information.

(B) Dates of issue, wearing and servicing, and suitable identification of persons responsible for these actions.

(C) Dates and conditions of tests and inspections.

(6) Employers shall supervise the respiratory protective program according to the following schedule:

(A) Observe at least monthly each employee wearing a non-emergency-use respirator while he is performing work tasks.

(B) Inspect each non-emergency-use respirator at least monthly.

(C) Inspect and test each emergency-use respirator at least monthly and after each use.

(D) Conduct a practice drill at least quarterly with each employee who would wear emergency-use respirators.

GROUP I

Group II requirements for Respiratory Protection apply with the following additions and changes:

(6) (A) and (6) (B) Inspection frequencies shall be at least weekly.

(7) Except for emergency-escape-use respirators, all respirators shall be a full-face, air-supplied or self-contained type, unless respirators of other types are certified under 30 CFR 11.

(8) Quantitative fit tests shall be administered to all employees who may be required to wear respirators.

Section 4 - Informing Employees of Hazards from Pesticides

GROUPS III AND II

(a) Before employees are exposed to any pesticide, pesticide formulation, inert, or raw material, they shall be fully apprised of the following:

(1) Identification by name, characteristics (smell, appearance, etc), and physical properties.

(2) Hazards of toxicity.

(3) Signs and symptoms of overexposure.

(4) Fire and explosion hazards.

(5) Precautions for safe handling.

(6) Emergency first-aid treatment for overexposure.

(7) Plant layout and emergency escape routes.

(b) Employees shall be trained in the use, limits of use, storage, and maintenance of all personal protective clothing and equipment which they may use.

(c) Employees shall be trained to recognize and control

the hazards arising from materials handling, housekeeping, waste disposal, and maintenance.

(d) Employees shall be trained in all emergency procedures.

(e) Employees shall be trained in the reasons for, and the practice of, personal hygiene.

(f) All training shall be conducted on a preassignment basis. Retraining shall be conducted semiannually or whenever necessitated by changes in equipment, processes, materials, or employee work assignments.

(g) A Material Safety Data Sheet, shown in Appendix V, or a similar form approved by OSHA shall be prepared for each pesticide or other chemical used or stored in the plant. A copy of each sheet shall be posted in a conspicuous place accessible to all employees.

GROUP I

Group II requirements for Informing Employees of Hazards from Pesticides apply, with the following change and addition:

(a)(8) A thorough explanation of all probable or suspect carcinogenic, neurotoxic, teratogenic, or reproductive health effects attributable to the pesticides to which workers may be exposed.

(h) A Material Safety Data Sheet shall be posted at all entrances for each Group I pesticide found in that area.

Section 5 - Work Practices

(a) Materials Handling

GROUP III

(1) General. No employee shall be permitted to routinely handle any pesticide with bare skin. Pesticides shall be handled in such a manner as to minimize their dissemination.

(2) Containers. All pesticides shall be handled in conformance with the labels on the containers as required in Section 2(a)(4). Any employee engaged in moving, filling, or emptying containers of pesticides shall wear the protective clothing and equipment as specified in Section 3. Emptied containers of pesticides shall be assumed to contain a residue of the material until decontaminated.

(3) Storage. Pesticides shall be stored in containers constructed and arranged so as to minimize leakage. Pesticide storage areas shall be so designated and separated from other plant areas. Such areas and containers therein shall be inspected at least quarterly to ensure that their integrity is not compromised. No person shall be permitted to eat, drink, smoke, or sleep in pesticide storage areas. Storage areas shall not be directly connected to adjacent work areas by heating ducts, ventilation ducts, doors, or windows.

GROUP II

Group III requirements for Materials Handling apply with the following change:

(3) Inspection frequency shall be at least monthly.

GROUP I

Group II requirements for Materials Handling apply with the following changes and addition:

(1) No employee shall be permitted to handle any pesticide with bare skin.

(3) Inspection frequency shall be at least weekly.

(4) Storage areas shall be of sound construction with restricted access.

(b) Housekeeping

GROUPS III AND II

(1) Areas where pesticides are manufactured, formulated, repackaged, stored, or otherwise handled shall be inspected at least daily for pesticide residues. Any equipment with pesticide leaks or residues shall be inspected for any indications of malfunction or structural damage, and such faults shall be promptly corrected.

(2) A pesticide that is spilled, leaked, or otherwise released shall be cleaned up or contained immediately. Fallout, condensates, and all other accumulations from airborne pesticide emissions shall be cleaned from employee work surfaces (such as handrails and workbenches) at least daily, and from all workroom surfaces (including walls, ceilings, and floors) at least monthly.

(3) Pesticides and pesticide-contaminated residues shall be flushed to a collecting sump, vacuumed,

absorbed by cleaning materials, or collected by other nondispersive means.

GROUP I

Group II requirements for Housekeeping apply with the following change:

(2) Workroom surfaces shall be cleaned at least weekly.

(c) Waste Disposal

GROUPS III AND II

(1) No disposal method shall be used which contravenes local, state, or Federal regulations.

(2) Pesticide-contaminated solids and liquids shall be decontaminated before disposal unless other approved disposal methods are used.

(3) Pesticide-contaminated waste gases shall be treated before release to the outside atmosphere to prevent return of pesticides into work atmospheres.

(4) Pesticide containers shall retain their warning labels until such time as they are decontaminated.

(5) Pesticide catch basins, drip pans, and other open collectors shall be checked regularly and emptied when necessary to prevent their acting as a secondary source of pesticide exposure.

GROUP I

Groups III and II requirements for Waste Disposal apply with the following change:

Delete (5). (Open containers should not be used to collect pesticide leakage. See Section 7, Part G.)

(d) Maintenance

GROUP III

(1) Employers shall institute a program of preventive maintenance which includes:

(A) Inspections, conducted at least quarterly, of all pesticide-processing equipment whose failure would subject employees to pesticide exposure. Lubrication, repair, or replacement of the equipment shall be performed whenever indicated by such inspections.

(B) Inspections, conducted at least quarterly, of ventilation systems and pesticide collection systems to ensure their maximum effectiveness.

(2) No pesticide-processing equipment shall be disassembled, opened, or otherwise modified or repaired in a manner which could expose any employee to the contents until the following precautions have been taken:

(A) The equipment shall be disconnected from sources of mechanical and/or electrical power and from flow of materials. Such cutoff shall be secured and posted.

(B) Any part of the equipment contaminated by pesticides shall be decontaminated, flushed, or purged prior to modification or repair.

(C) Employees performing modifications, repair, or maintenance shall wear appropriate personal protective

clothing and equipment.

(3) All newly installed, repaired, replaced, or reassembled pesticide-handling equipment shall be tested for leaks and mechanical function before being returned to general use.

(4) No employee shall be allowed to enter a vessel or confined space without first obtaining a permit signed by the supervisor.

(5) The supervisor shall not sign an entry permit until the following have been completed:

(A) The flow of material to the space has been cut off, the cut-off valve secured by the lock of each worker to enter the confined space, and the area posted.

(B) The area has been thoroughly flushed, ventilated, and tested for the concentration of oxygen.

(6) The employee entering the space shall use appropriate personal protective equipment and shall also wear a lifeline.

(7) During the time period that an employee is working within a confined space, visual and voice contact shall be maintained with a second person outside the space. That second person shall also be equipped with a lifeline and appropriate personal protective eguipment and shall be in contact with a third person.

GROUP II

Group III requirements for Maintenance apply, with the following addition and changes:

(1)(A) and (1)(B) Inspection frequencies shall be at least monthly.

(1)(C) Keeping written records of maintenance, repair, and replacement histories of process equipment as long as the equipment is on the plant site. The records shall be used to determine a schedule of servicing and component replacement that is frequent enough to avoid equipment failures.

GROUP I

Group II requirements for Maintenance apply with the following changes and addition:

(1)(A) and (1)(B) Inspection frequency shall be at least weekly.

(2)(D) Local lubrication and other minor maintenance procedures performed on closed systems shall be carried out only when appropriate employee protection is provided.

(e) Emergency Procedures

GROUPS III AND II

(1) First Aid. Emergency first-aid services shall be established to provide care to any worker manifesting effects of pesticide exposure. Whenever possible, first-aid services shall be delivered by persons trained in emergency medical services. Records of such services shall be included in the employee's medical history and other plant medical records. These services shall include but not be limited to:

(A) Deluge showers and eyewash fountains

within close proximity to all locations where exposure to pesticides may occur including, but not limited to, packaging, unpackaging, maintenance, loading and unloading areas, and sampling ports. These facilities shall be checked periodically to make certain they are operating properly and have not been contaminated. All runoff from use of showers and eyewash fountains shall drain to a sump for decontamination. Pathways leading to showers and eyewash fountains shall be kept free of all obstacles.

(B) Provisions for emergency transportation to health care facilities.

(C) Oxygen and resuscitation equipment.

(2) Provisions for medical treatment of overexposure to pesticides shall be made, including appropriate arrangements with a local physician, clinic, or hospital.

(3) Leaks and spills

(A) Materials for absorption or hoses with running water shall be available so that spilled or leaked pesticides may be removed from work areas for decontamination, disposal, or reuse.

(B) Emergency-escape personal protective equipment shall be readily available to employees working in areas where leaks or spills may occur.

(C) Employers shall provide for the warning and evacuation of employees in the case of leaking gasecus pesticides.

(4) Fire and Explosion

(A) A system for informing employees and notifying fire-fighting personnel in case of fire shall be installed.

(B) Personal protective equipment and first-aid supplies shall be available in the plant for dealing with exposure to the materials formed by combustion and pyrolysis of pesticides.

(C) Fire-fighting personnel shall be provided with a map and data reflecting all information obtained by the employer in Section 8(a)- Monitoring.

(D) Drills shall be conducted to thoroughly familiarize employees with escape, rescue, fire-fighting, and power- and materials-shutoff procedures in case of fire.

(5) All procedures in Section 5(e) - Emergency Procedures shall be incorporated in a written emergency action plan.

GROUP I

Group II requirements for Emergency Procedures apply with the following changes:

(3)(B) Emergency-escape personal protective equipment shall be carried by employees or shall be immediately at hand for employees working in areas where leaks or spills may occur. Emergency rescue equipment shall be available just outside such areas.

(3)(C) Employers shall provide a warning system for informing employees of leaking pesticide gases or

vapors. Such a system may include continuous monitors connected to audible alarms, pressure-loss sensors coupled with visual indicators, etc. The system must be capable of warning all potentially exposed employees before a hazardous concentration is reached. Warning systems shall be tested at least monthly.

Section 6 - Sanitation and Personal Hygiene

GROUP III

(a) Eating and food preparation or dispensing (including vending machines) shall be prohibited where there is occupational exposure to pesticides.

(b) Smoking shall be prohibited in areas where pesticides are present.

(c) Employees who handle pesticides or equipment contaminated with pesticides shall be instructed to wash their face, hands, and forearms with soap or mild detergent and water before eating, drinking, smoking, or using toilet facilities.

(d) To prevent skin absorption of pesticides, employers shall instruct employees not to use solvents to clean their hands or other exposed areas of the body.

(e) The employer shall provide clean change rooms equipped with storage facilities for street clothes and separate storage facilities for protective clothing and equipment whenever employees are required to wear protective clothing and equipment in accordance with Section 3.

GROUPS II and I

Group III Requirements for Sanitation and Personal Hygiene

apply, with the following change and additions:

(e) Employees occupationally exposed to pesticides shall not wear work clothing away from their place of employment.

(f) Facilities for shower baths shall be provided for employees occupationally exposed to pesticides. Workers should shower before changing into street clothes.

(g) Employers shall instruct employees exposed to pesticides to wear clean work clothing daily, and cleaning establishments shall be informed as to the hazards of handling pesticides and proper disposal procedures for pesticide-contaminated wastewater.

(h) A separate walled change area for removal and storage or disposal of contaminated clothing with exit to shower shall be provided.

(i) Showers with potable warm running water shall be provided. The exit from showers shall open into a clean change area free from pesticide contamination.

Section 7 - Engineering Controls

GROUPS III AND II

Employee exposure to pesticides, intermediates, and solvents shall be minimized through the use of engineering controls and work practices.

(a) Engineering controls shall be used to seal or isolate process equipment in order to minimize the escape of pesticides into the workplace. In the case of isolation, appropriate ventilation shall be used to prevent the accumulation

of pesticide emissions.

(b) Local exhaust ventilation shall be used to control airborne process emissions which are not amenable to control by sealing or isolation. These ventilation systems shall be vented to appropriate air cleaning devices.

(c) Appropriate measures shall be implemented in order to prevent any leakage of liquid process streams from spreading into the workplace. These measures may include the use of physical barriers such as containment dikes or splash shields in addition to specified work practice cleanup and decontamination procedures.

(d) Threaded pipe connections shall not be used for pesticide-contaminated streams.

GROUP I

Group II requirements for engineering controls apply, with the following additions:

(e) Process leaks shall be minimized through the selection of hardware which presents a minimum potential for leakage consistent with the required process performance. Types of hardware may include internally pressurized double mechanical seals, "canned" pumps, welded pipe connections, or pressure-tested piping and vessels (at least 2.5 times maximum working pressure). Emissions from all potential process leak points shall be controlled, including but not limited to:

(1) Seals on pumps, vessel agitator shafts, mixer drive shafts, compressors and other similar pieces of equipment.

(2) Valves, including process control valves.

(3) Flanges, gaskets, and other such connections.

(4) Process piping and reactor manways.

(f) Where possible, process and piping systems shall be designed such that anticipated equipment failure or operator errors will not result in workplace emissions of pesticides. For example, pressure relief valves on positive displacement pumps may be piped to release to the pump intake. Automatic process control valves may be installed so that failure would occur in a fail-safe (non-emission) position. Automatic cutoff valves actuated by level indicators on receiving vessels may be installed on process pumps.

(g) In the case of process leak points which cannot be eliminated using the procedures outlined in (e) and (f) above, controls shall be implemented so that leaks can be detected and controlled immediately in order to minimize occupational exposure. These controls may include a series of flexible local exhaust takeoffs to be used on an "as needed" basis, warning devices to detect loss of pressure in the internal pressurizing fluid of double mechanical seals, or similar controls.

(h) Ventilation ductwork and pneumatic transfer systems for pesticides shall be under negative pressure during operation. Exhaust air from ventilation or pneumatic transfer systems shall not be recycled to the workplace, either intentionally or through inadvertent positioning of air intakes in relation to exhaust vents.

(i) Chemical sewers or sumps shall be kept sealed or shall be eguipped with appropriate one-way flow devices to

prevent the evaporation of pesticide vapors into the workplace.

Section 8 - Monitoring and Recordkeeping

(a) Monitoring

GROUPS III, II, AND I

(1) Employers shall conduct a survey of the plant to determine:

(A) The names and approximate quantities of all pesticides used or stored in the plant.

(B) Places where pesticides might escape from containers or equipment and the expected distribution of pesticide contamination in the event of such escape.

(C) All locations and operations in which employees may be exposed to pesticides and the nature of their potential exposure. Airborne concentrations of pesticides to which workers are exposed shall be measured.

(D) The movement and location of pesticides in plant processes and storage.

(2) The survey shall be repeated at least annually.

(b) Recordkeeping

GROUPS III, II, AND I

(1) The following records shall be maintained by the employer for at least 30 years after termination of employment of the employee:

(A) Survey data from Section (a) -

Monitoring.

(B) Medical examinations.

(C) Emergency treatment.

(D) Documentation of overexposure of any employee to pesticides or any other chemical in the workplace.

(2) All records shall be stored and accessible in a manner that permits comparison between medical records and exposure data.

(3) Medical records shall be made available to designated medical representatives of the Secretary of Labor, of the Secretary of Health, Education, and Welfare, and of the employee or former employee.

II. INTRODUCTION

This report presents the criteria and the recommended standard based thereon which were developed to protect employees engaged in pesticide manufacturing and formulating operations against occupational illnesses. The criteria and the resulting standard have been designed to afford improved worker protection from exposures to pesticide active ingredients and to other substances used in manufacturing and formulating processes, such as raw materials, intermediates, inerts, and solvents. The criteria document fulfills the responsibility of the Secretary of Health, Education, and Welfare, under Section 22(c)(1) of the Occupational Safety and Health Act of 1970, to "...develop and establish recommended occupational safety and health standards..."

NIOSH, after a review of data and consultation with others, formalized a system for the development of criteria upon which standards can be established to protect the health and to provide for the safety of workers exposed to hazardous chemical and physical agents. These criteria and the recommended standard for occupational exposure to pesticides during their manufacture and formulation are part of a continuing series being developed by NIOSH. The methodology of this study consisted of developing, evaluating, and recording information from literature searches,

from visits to pesticide manufacturing and formulating plants, and from consultations with external sources including other Federal agencies, professional occupational health societies, and an advisory group. The advisory group consisted of knowledgeable individuals from industry, labor, government, and academia. These sources assisted NIOSH by identifying additional information for consideration and by reviewing the adequacy and soundness of the critique of existing scientific information and the feasibility of the recommended standard based thereon. A draft of the criteria document was reviewed in March 1978 by the advisory group.

The recommended standard is intended to protect against development of systemic and local adverse health effects, and to be attainable with existing technology and techniques. Emphasis has been placed on effective work practices, engineering controls, employee training, and medical surveillance. Permissible exposure limits have not been developed in this document; however, NIOSH recommends compliance with promulgated Federal occupational exposure limits (see Appendix III) and adoption of new environmental limits in those cases where the NIOSH recommended limit differs from those already promulgated. These include the environmental limits recommended for substances such as parathion, methyl parathion, creosote, ethylene dibromide, and dinitro-o-cresol (see Appendix IV).

The standard is not intended to inhibit flexibility in the way a task is performed or to restrict the development of safer techniques. Instead, any criteria and recommended standard

should encourage management and labor to develop safer equipment, more effective work practices and engineering controls, and more appropriate training programs that will result in more healthful work environments. Simply complying with the recommended standard should not be the final goal.

The criteria and recommended standard were developed from an overall process point of view and are designed to protect employees from exposure to pesticides and other substances used in the manufacture and formulation of pesticides. The document specifies proper work practices as a means of minimizing the risk of adverse health effects and identifies appropriate biologic monitoring and medical surveillance programs for employees who work with pesticides during their manufacture and formulation. The recommended standard indicates the importance of providing a clean workplace and of apprising all employees of the hazards of pesticides and of the need to utilize proper work practices. Within each of the eight sections of the recommended standard, requirements vary according to the pesticides to which they apply: (1) the most strigent work practices and engineering controls are specified for Group I pesticides, which pose a significant risk of adverse acute health effects at low concentrations, or risk of carcinogenic, teratogenic, neurotoxic, or reproductive effects; (2) less stringent requirements apply to Group II pesticides which pose adverse acute health risks at moderate doses; and (3) the least stringent practices and controls are specified for Group III pesticides, which, based on present data, pose minimal risk of adverse acute effects even at

relatively high-dose levels. The basis for establishing these three groups and for assigning pesticides to each is contained in Chapter VI, along with a discussion of the rationale for selecting specific work practices and control requirements for each group.

These criteria for a pesticide standard apply only to occupations in pesticide manufacturing and formulating. This includes manufacturing, formulating, packaging, mixing, blending, or repackaging of any pesticide active ingredient. Application of this recommended standard to situations other than the occupational settings specified above is not warranted.

The development of the recommended standard for the manufacture and formulation of pesticides has revealed that additional research is needed in the following areas: (1) studies to determine whether particular pesticidal chemicals have carcinogenic, teratogenic, mutagenic, neurotoxic, behavioral, or other dealyed toxic effects, (2) effective decontamination of work clothing, (3) more effective engineering controls to limit pesticide emissions and exposures in manufacturing and formulating processes, and (4) more effective personal protective equipment and clothing for pesticide workers. A more complete discussion of these and other research areas is presented in Chapter VII.

III. HEALTH HAZARDS FROM EXPOSURE IN PESTICIDE MANUFACTURE AND FORMULATION

As defined by the Federal Environmental Pesticide Control Act (FEPCA), a pesticide is (1) "any substance or mixture of substances intended for preventing, destroying, repelling or mitigating any pest (insect, nematode, fungus, weed, other forms of terrestial or aquatic plant or animal life or viruses, bacteria, or other microorganisms, except microorganisms on or in man or other living animals) which the Administrator (EPA) declares to be a pest, and (2) any substance or mixture of substances intended for use as a plant regulator, defoliant or dessicant" (40 CFR 162). There are approximately 1,500 active ingredients in common use and registered by EPA (Federal Register 41:7218-7375, February 17, 1976). There are also numerous other pesticide active ingredients for which tolerance levels on food have been established, which are registered on an experimental basis only at this time, or which are produced in the United States for export. These substances range in acute toxicity from lethal at low doses (strychnine) to edible in relatively large quantities (sodium chloride). Certain of these compounds have produced carcinogenic, teratogenic, mutagenic, and neurotoxic effects, and alteration of reproductive processes or functions in experimental animals. Consequently, this chapter is not intended

to be a comprehensive review of any individual pesticide or to cover the biologic effects of any substantial fraction of the total number of substances currently registered and used as pesticides.

The earliest known pesticides were organic materials of natural origin. Inorganic compounds, particularly the salts of arsenic, lead, mercury, copper, and zinc, came into wide use as pesticides in the mid-19th century. The era of synthetic organic pesticides began with the discovery of the insecticidal activity of dichlorodiphenyltrichloroethane (DDT) in 1939. The success of DDT during World War II against lice carrying typhus and against mosquitos carrying malaria created great enthusiasm for commercial use when the war ended. Subsequent research developed a wide variety of synthetic organic pesticides, including the organochlorine (OC), organophosphorus (OP), and carbamate pesticides. The 1,500 active pesticide ingredients are now formulated into more than 40,000 registered pesticide products [1].

Since the discovery and use of pesticides, their potential for producing harmful effects in humans has been recognized along with their beneficial effects. This recognition has resulted in a vast expenditure of government funds for scientific research and in a voluminous amount of literature pertaining to the biologic effects of pesticides. Much has been learned of the biologic effects of these substances, but the research effort has been disappointing in some important respects. For instance, probably no substance has been more intensively studied than DDT,

especially in terms of potential for carcinogenic effects. Yet, it is unknown whether the very small amounts of DDT to which we have all been exposed are responsible for any portion of the overall human cancer problem.

While the results of studies on the effects of exposure of humans to small quantities of DDT and other pesticides remain inconclusive, larger exposures to certain pesticides are conclusively harmful. The recent incidents of severe neurologic disorders in employees involved in the manufacture of Kepone and leptophos provide clear evidence of harmful effects. Based on these episodes and other less spectacular incidents discussed later in this chapter, every effort must be made to minimize human exposure to pesticides, especially during their manufacture and formulation when the opportunity for excessive exposure is potentially the greatest.

In the development of pesticides today, an effort should be made to achieve a selective toxic effect by exploiting physiological and biochemical differences between cells of pest organisms and those of nontarget organisms. Such differences are infreguent and are overshadowed by the abundance of similarities existing among most species. Moreover, while a particular substance may be thought of as having one main toxic action, eg, inhibition of chitin synthesis in insects, the normal functions of the mammalian body involve so many enzyme systems and physiologic interactions that the probabilities are high that the substance may also affect mammalian systems.

DDT, at the time of its development as an insecticide, was

one of the two substances (the other being penicillin) thought to have achieved the ultimate in selective action. A very high ratio exists between the acute toxicities of DDT for the mosquito and for man. However, recent research has demonstrated that the compound is capable of producing tumors in some species of experimental animals [2]. Furthermore, there is convincing evidence that DDT and its metabolites accumulate in food chains by a process of biologic concentration in ecosystems [3]. These findings have severely limited the acceptability of DDT use in many countries.

Similarly, when mirex was developed as an effective weapon against the fire ant a few years ago, it was believed to be a safe pesticide with regard to man and the environment. However, recent animal tests indicate this substance is a carcinogen [4,5], further demonstrating that pesticides, although specifically designed to attack undesired insects and other pests, present potential hazards to human beings.

Observations in both humans and experimental animals have clearly shown the ability of certain pesticides to produce delayed irreversible effects. Induction of cancer in humans is a primary concern, and may require as many as 20-40 years to appear. Due to the inability to detect most cancer and to relate it to a specific etiologic agent, as well as a desire to prevent its occurrence, the results of animal studies must be relied upon extensively in assessing the toxic effects of pesticides. The same argument holds for other types of delayed actions including carcinogenesis, mutagenesis, teratogenesis, other effects on

reproductive processes, chronic toxic effects on parenchymatous organs, eg, aplastic anemia, chronic nephrosclerosis and cirrhosis, and interference with neuronal integrity.

Industry Characteristics and Extent of Exposure

(a) Pesticide Production

In 1975, the latest year for which figures are available, 1.61 billion pounds of pesticide active ingredients (excluding creosote) were produced in the United States, an increase of 13.5% over 1974 [1]. Of this total, 788 million pounds were herbicides, 666 million pounds were insecticides, and 156 million pounds were fungicides [1]. The growth in pesticide production is expected to continue according to a 1976 survey conducted by the US Department of Agriculture's (USDA) Economic Research Service [6]. Expansion in the industry should boost domestic capacity in 1976 by 12% and by another 7% by 1978 [1].

Approximately 90% of all present-day pesticides are organic compounds. Insecticides consist primarily of OC, OP, and carbamate compounds. Fumigants include halogenated hydrocarbons and inorganic gases. Herbicides include amides, arsenicals, carbamates and thiocarbamates, OP compounds, and substituted ureas. Fungicides include thiocarbamates, phthalimides, and orgarotin compounds. The production of these compounds involves many chemical processes including chlorination, alkylation, nitration, phosphorylation, sulfonation, and bromination.

Creosote, a mixture of phenols derived from either wood or bituminous coal by destructive distillation, is used as a wood

preservative because of its ability to kill both the fungi and the boring insects and arthropods that are likely to infest wood. In 1972, approximately 1.15 billion pounds of creosote were produced, an amount almost equal to the total amount of synthetic organic pesticides produced that year [7].

Inorganic pesticides account for the remaining 10% of pesticide production and include calcium arsenate, lead arsenate, sodium flouride, arsenic acid, borate, and sulfur. Of all inorganic pesticides, 55% are fungicides, 38% are herbicides, and 7% are insecticides [1]. The estimated 1975 production levels and uses of major pesticides are shown in Table XIV-1.

(b) Description of Industry

Commercial pesticide products are produced in two sequential operations: manufacturing and formulating. The manufacturing operation produces the active pesticide ingredients by chemical synthetic procedures. The active ingredients are then transformed into formulated products by diluting them with solvents, by spraying them onto clay, or by mixing them with other carriers. By their nature, formulating operations are primarily batch mixing and blending operations [8(pp 1,70)].

(1) Pesticide Manufacturers

Pesticide manufacturers usually operate capital-intensive, integrated chemical synthesis plants and, with a few exceptions, produce many other chemical products in addition to pesticides. In 1972, the average pesticide manufacturing plant employed approximately 185 workers, 100 of whom were employed directly in production operations [9]. The

employees normally include chemists, engineers, managers, skilled chemical operators, pipefitters, electricians, and laborers.

Manufacturing includes pretreatment of reactants (change of size, temperature, and state), reaction, purification, and post-treatment of products (change of size and state). Raw materials for manufacture are delivered in bulk by pipeline, railroad car, barge, etc, or may be produced in-plant, often as by-products of other reactions. Manufacturers may produce several pesticide active ingredients at a single plant, and such a plant usually consists of several separate but interconnectable production areas or subplants. A subplant contains the equipment necessary for carrying out all the unit processes and operations, such as reaction, distillation, filtration, and mixing, which are necessary to synthesize a product from raw materials. Subplant hardware may include mills, screens, hoppers, tanks, reactors, absorption columns, cooling towers, stills, filters, centrifuges, dryers, etc. Process monitoring, sampling, and analysis are performed to determine temperatures, pressures, flowrates, densities, and composition changes in order to control the chemical reactions.

(2) Pesticide Formulators

Pesticide formulating establishments are generally smaller than manufacturing establishments. The average formulator employs 32 workers, 18 of whom are employed in production [9]. Employees may include engineers, chemists, operators, and laborers. There are major variations among formulators both in size and in operating practices. Seventy-one

percent of all formulating establishments employ less than 20 employees [9]. Cnly 6% of all establishments employ more than 100 employees [9], but these larger plants dominate total production. Formulators with 100 or more employees account for 56% of production, whereas formulators with less than 20 employees account for only 12.5% of all production [9].

A formulating operation is generally less complex than a manufacturing operation. Usually, a formulator receives concentrated active ingredients from a manufacturer or a customer and dilutes them with various nonpesticidal materials known as "inerts." The term inert refers to the effect of the substance on the target organism relative to the effect of the pesticide on that organism. However, as with any chemical, a toxic effect can be obtained with any inert at some dose, and many so-called inerts are more toxic to man than the term would lead one to believe. The formulating process may also include physical or chemical treatment to yield particular product forms: dust, powder, wettable powder, granule, pellet, emulsifiable concentrate, or aerosol. Further processing may be done by wholesalers, retailers, repackagers, or end users. With a few exceptions, formulating is a simple process varying in type according to the desired end product [8(pp 1,11,12,7)].

The preparation of dust and powder pesticide formulations entails dispensing from hoppers, screening for size, and mixing with flour, silica, sulfur, lime, gypsum, talc, or clay in a hammer mill, roller mill, or other type of mill. Granule-formulating consists of dispensing and sizing the inert,

eg, clay, vermiculite, ground corncobs, diatomaceous earth, dissolving or melting the pesticide in a tank, and then spraying the pesticide onto the inert in a mixer [8(pp 1,11,12,34,35)].

Liquid formulations are generally prepared by placing both a pesticide and a solvent into a mixing tank provided with some type of agitator. The resultant liquid may be filtered or decanted to remove insoluble material.

The care exercised in substance handling and control during formulation varies greatly from the relatively sophisticated procedures and equipment found in a major facility where both manufacturing and formulating occur [8(pp 52-62)] to less complicated setups where, for example, second-hand equipment is used [8(pp 11-18)]. Chapters IV and V provide additional details on the manufacturing and formulating processes, work practices, and control processes.

(c) Industry Statistics

The Standard Industrial Classification Codes (SIC's) for establishments primarily involved in the manufacture and formulation of pesticides are:

(1) SIC 2869 - Manufacture of pesticide and other organic chemicals, not formulas; and

(2) SIC 2879 - Agriculture chemical manufacturers and formulators--including insecticides, herbicides, agricultural chemicals, household insecticides, and agricultural chemicals not otherwise classified.

The most recent Bureau of Census statistics (Table XIV-2) for these two industries show that there were 19 manufacturing

establishments and 388 formulating establishments in 1972 identified as primarily producing pesticides. Eighty-one percent of the value of shipment from all manufacturing and formulating establishments originated at these facilities. The remainder was produced at 6,679 other establishments, which produce pesticides as secondary products. These establishments are in a number of industries such as Industrial Organic Chemicals (SIC 286), Polishes and Sanitation Goods (SIC 2842), Plastic Materials and Resins (SIC 2821), Pharmaceutical Preparation (SIC 2834), and Industrial Inorganic Chemicals (SIC 281).

The geographic distribution of pesticide production in the US is shown in Table XIV-3. The greatest amounts of pesticides are produced in the South, followed by the North Central region. The South also has the largest number of formulating establishments (Table XIV-2), reflecting the region's high agricultural production. The value of shipment data in Tables XIV-3 and XIV-4 reveal that although the Western region has approximately 25% of the primary formulating establishments, they appear to be smaller than those found in other parts of the US, due to the low value of shipment for this region (11%). Conversely, the formulating establishments found in the North Central region are relatively larger than those found in other parts of the country. This region shipped 41% of dollar value from just 25% of US formulating establishments.

(d) Estimates of Worker Population

Table XIV-4 shows that approximately 8,700 production workers are employed in establishments identified as primary

manufacturers and formulators of pesticides. Of this total number of production workers, 1,900 work in manufacturing plants and 6,800 work in formulating plants.

In Table XIV-5, the distribution of formulating plant workers is shown by size of the formulating plant. Approximately 1,000 workers are employed in plants that have less than 20 employees, and another 2,100 workers are employed in plants that have between 20 and 95 workers.

To estimate the number of production workers exposed in other establishments producing pesticides as secondary products is difficult. However, in these industries there are over 350,000 additional production employees who have the potential for exposure because they work at a plant that produces pesticides [9].

Pesticide Properties and Worker Exposure Routes

The particle size, volatility, and solubility of materials present during the manufacture and formulation of pesticides significantly affect environmental concentrations and accessibility to the possible routes of entry of potentially exposed workers. The following descriptions are of specific chemical and physical factors involved in the major routes of pesticide exposure.

(a) Inhalation Exposure

The inhalation of pesticide dusts, vapors, mists, and gases may present a significant occupational hazard. Dust hazards are created by dry formulations that involve granules,

wettable powders, baits, and soluble powders. For example, captan, carbaryl, and chlorda are usually formulated in powder form, whereas chlorpyrifos and diazinon are often formulated in granular form. Exposure to pesticide vapor can occur in the production of fumigants such as ethylene dibromide, acrylonitrile, and trichloroethylene, and some fumigants, such as phosgene and ethylene oxide, are gases at standard temperature and pressure (STP). Although the carriers used in formulating pesticide dusts are described as "inerts" with respect to pesticide potency, several may present health hazards; for example, talc may contain asbestiform fibers.

In pesticide operations, dusts are generated by the mechanical agitation of solid materials as in packaging and milling. Hammer-mill grinding has been shown to produce powders with average particle sizes up to 75μ. Air-mill grinding creates micronized particles of 2-5μ[10].

Retention of particles within the lungs depends on many factors: size, shape, hygroscopicity, density, reactivity, and nasal or oral inhalation [11]. Hayes [11] speculated that in the absence of specific information on a particulate, it can be assumed that about 25% of inhaled material would be exhaled, about 50% would be deposited in the upper respiratory passages and subsequently swallowed, and about 25% would be deposited in the lower respiratory passages.

Several studies have been conducted to measure worker respiratory exposure during pesticide manufacture and formulation. Comer et al [12] reported that formulating plant

workers had higher potential for body-front exposure than did spraymen. Tests were conducted in three formulating plants during formulation of 4 and 5% carbaryl dusts. The workers studied were at bagging or mixing stations, areas of greatest potential contamination. Considerable variation was observed in the range of exposure values for each work activity. One of the factors observed as causing occasional high values of exposure was malfunctioning of the bag-filler spout mechanism, resulting in excess billowing dust. The formulation plant workers' mean respiratory exposure was 1.1 mg/hour of work activity. The amount of pesticide entering the body via the respiratory route was estimated from the contamination of special filter pads used in place of the usual outer absorbent filter pads which cover the filter cartridges of the respirators worn. To compare values, tests were also conducted on spraymen operating tractor-drawn airblast equipment as they applied 0.045-0.6% carbaryl spray to fruit orchards. For spraymen the mean exposure value was 0.09 mg/hour. It is reasonable to assume that the higher amounts inhaled by formulators reflect their frontal exposure to concentrated dry carbaryl dust, and that spraymen inhaled and consequently absorbed lesser amounts due to the larger size of the spray droplets.

In another study, Jegier [13] measured respiratory exposure of formulation plant workers during the formulation of 25% azinphos-methyl wettable powder. Air samples were taken in the breathing zone of the plant workers during the formulation process. Respiratory exposure was determined directly from the

quantities of azinphos-methyl deposited on filter pads attached to double-filter respirators. The concentrations in the air sample ranged from 1.07 to 9.64 mg/cu m. The filter pads held amounts from 0.72 to 8.24 mg/day. The highest concentrations were recorded in the blending area of the plant.

Hayes [14] reviewed the relationship between physical forms and the exposure hazards of the three major types of pesticide formulations (gases, dusts, and sprays). He found that materials in the form of a gas, vapor, or very fine particulate were inhaled more efficiently than are larger particles, and he concluded that the most hazardous form for respiratory intake was a gas, while dusts and then sprays followed in decreasing order of hazard potential. This effect of particle or aerosol size on exposure was further studied in agricultural spraymen by Wolfe et al [15] who concluded that the smaller aerosol particles (20-100μ diameter) generated by a concentrate-spray apparatus compared with those produced by a conventional spray machine (over 150μ diameter) resulted in increased potential exposure through the respiratory tract. The mean respiratory exposure by the concentrate-spray technique was 0.05 mg/hour while by the conventional dilute-spray method the mean was 0.02 mg/hour. The concentration of the pesticide in the preparation being sprayed was also mentioned as a factor to be considered in the assessment of potential exposure.

Pesticides have a wide range of vapor pressures, varying from nonvolatile materials, such as DDT and dieldrin, to compounds with extremely high vapor pressures, such as methyl

bromide. The volatility of the material affects the environmental concentration and, thus, is a significant factor in respiratory exposure.

Dichlorvos (DDVP), an OP compound, is an example of a highly volatile pesticide. Because of this property, DDVP is frequently formulated with wax or other suitable materials from which it is slowly released. Its high vapor pressure may cause large concentrations to accumulate in the air of the workplace during manufacturing and formulating operations. Menz et al [16] measured the exposure of factory workers to DDVP in the production and processing of a DDVP-releasing aerosol product. Measurements were taken in the vaporizer production and packaging room for 8 months, and DDVP levels ranging up to 3 mg/cu m were detected. Although the various measurements revealed considerable fluctuations, on the average, the employees were exposed to DDVP concentrations of 0.7 mg/cu m on each working day of the experimental period.

Many incidents of poisoning due to respiratory exposure to a variety of pesticides have been reported in the literature and are discussed later in this chapter. These incidents demonstrate the need to protect workers from this exposure mode. The experience with methomyl [17] shows that problems due to toxicity can be avoided by controlling the form of pesticides and by reducing the inhalation hazard. Methomyl is a highly toxic carbamate pesticide which was introduced in California in 1969 as a water-dispersible powder of 90% concentration. Shortly thereafter, a number of poisoning cases occurred in which

methomyl was implicated as the causative agent. These cases included acute intoxications in formulation plant workers and farm laborers from inhalation of the powder. Subsequently, a liquid formulation of methomyl was introduced to avoid exposures that resulted from handling the light pesticide powder, and this resulted in fewer methomyl poisoning incidents.

(b) Dermal Exposure and Absorption

Workers frequently experience dermal exposure to pesticides with subsequent absorption through the skin. Exposure studies of formulators [12] and agricultural workers [13] have shown that dermal exposure to pesticides occurs frequently if proper precautions are not taken. Wolfe and Armstrong [18] reported the dermal exposures of workers to DDT in two formulating plants. Highest exposures occurred at the bagging station where the mean dermal exposure was calculated to be 524.5 mg/hour. Comer et al [12] observed that carbaryl formulating plant workers received a mean dermal exposure of 73.9 mg/hour of work activity. Jegier [13] reported dermal exposure to azinphos-methyl by formulation workers in the blending area based on quantities of the pesticide collected on cellulose pads attached to workers' foreheads. The exposure levels ranged from 39.2 to 167.2 mg/day with a mean of 80.9 mg/day.

The rate at which a particular compound is absorbed through the skin is determined by the nature of the compound itself, by the condition of the skin, and by external factors such as temperature [11]. One major factor is the solubility of the pesticide. Lipid-soluble compounds, eg, parathion, DDT,

aldrin, and toxaphene, are absorbed more readily than water-soluble materials [11]. The most rapid and complete absorption through the skin occurs with chemicals which have some solubility in both water and lipid [19].

Skin absorption for any given compound is also proportional to the skin area exposed, and dependent upon the region exposed. Furthermore, different portions of the human skin absorb chemical substances at different rates. Maibach and coworkers [20] used 14C-labeled parathion to compare absorptive capacities of different parts of the human body. The results (see Table III-1) indicate that under experimental conditions the greatest rate of absorption and the most complete uptake in the male was through the scrotal skin where approximately 100% of the applied dose was absorbed. The possibility of pesticide being completely absorbed through the scrotal skin emphasizes the need for increased concern for protection of this area. Another area of the body where absorption was higher than expected was the head and neck, where 32-47% of the applied parathion dose was absorbed compared with approximately 9% for the forearm.

A major factor that may alter both the degree and rate of skin absorption is the condition of the skin barrier itself [11]. The skin barrier may be injured, thereby leading to increased absorption, by a number of factors including washing with organic solvents, irradiation, and thermal or chemical burns [11].

TABLE III-1

ABSORPTION OF PARATHION FROM
VARIOUS PARTS OF THE BODY

	Urinary 14C Excretion Expressed as Percent Applied Dose	Ratio to Forearm
Forearm	8.6 ± 5.6	1.0
Palm	11.8 ± 4.0	1.3
Abdomen	18.5 ± 11.5	2.1
Back of the Hand	21.0 ± 8.1	2.4
Scalp	32.2 ± 6.1	3.7
Forehead	36.2 ± 12.6	4.2
Ear Canal	46.5 ± 17.7	5.4
Axilla	64.0 ± 32.5	7.4
Scrotum	101.6 ± 18.8	11.8

Adapted from reference 20

Dermatitis and eczema also decrease the effectiveness of the skin barrier and increase uptake [21]. Increased circulation of blood through the dermis of the skin by physical movement and sweating also enhance the intake from the surface of the skin [11]. Very fine powders tend to be absorbed more readily than coarser powders rubbed on the skin in exactly the same way. Hayes [11] found that very finely ground technical dieldrin was absorbed as readily as dieldrin applied to the skin in solution; in contrast,

coarsely ground dieldrin powder was not as well absorbed. The particle sizes of the powders were not specified.

Solvents, binders, and inert materials used in pesticide manufacture and formulation also have an effect on pesticide dermal absorption and toxicity. For example, Brown [21] recorded significant changes in the LD50's of two experimental samples of carbamates (composition proprietary) in CFE strain rats with varying solvents, because of differences in dermal absorption. The different solvents tested included acetone, N-methylpyrrolidone, and xylene. The first sample of carbamate in acetone at a concentration of 20% resulted in an LD50 of >1,000 mg/kg compared with one of 100-200 mg/kg when the carbamate was dissolved in N-methylpyrrolidone at a concentration of 25%. A different sample of carbamate in acetone at a concentration of 20% yielded an LD50 of >100 mg/kg in males and 100 mg/kg in females, compared with ones of 10 mg/kg in males and <3 mg/kg in females obtained when a 5% solution in xylene was used. Increase in absorption may involve a solvent that by its own ready absorption helps to carry the toxicant through the skin. Injury to the skin by these agents may also increase dermal absorption.

Adherence of pesticides to the skin was demonstrated by Fredriksson [22] who studied the decontamination of human skin exposed to parathion. Using 32P-labeled parathion, applied to the skin of four volunteers, he demonstrated that a soap and water wash for 30 seconds removed only 36-48% of the remaining parathion if the wash was delayed for 6 hours. A wash with

alcohol, in which parathion is soluble, still allowed 10% of the dose to remain after the same amount of time.

In summary, for many pesticides, especially the OC, OP and carbamate insecticides, exposure via the dermal route is one of the most important sources of exposure. Extra care should be taken to protect all areas of the skin from exposure to percutaneously absorbable compounds, and employees should be well aware of the hazards of dermal absorption of pesticides.

(c) Gastrointestinal Absorption

Oral exposures occur through accidental splashing of liquid pesticides into the mouth, by smoking or eating with pesticide-contaminated hands, by rubbing the mouth area with contaminated hands, and by swallowing inhaled material that may have entered the upper respiratory tract or have been swept up the trachea by ciliary action into the pharynx. However, such oral exposures are difficult to measure or quantify.

The esters of such acids as 2, 4-D and 2, 4, 5-T would be expected to be hydrolyzed within the intestinal tracts of mammals, so that the free acids would be the entities to be absorbed through the walls of the tract. Both 2, 4-D and 2, 4, 5-T are weak acids, with pK's at 25C of 3.31 and 3.14, respectively, and are soluble in lipids and lipid solvents. Such compounds would be expected to be essentially nonionized in stomachs, where the pH is between 1.0 and 2.0, and to be well absorbed, therefore, from the stomach and the first portion of the duodenum [23,24]. As the pH of the contents of the intestinal tract rises after the influx of the succus entericus

and the pancreatic secretions, these compounds would become more ionized and, consequently, less lipid soluble and less well absorbed. Absorption would occur by the process described by Palay and Karlin [25] of pinocytosis into the mucosal cell, collection in the endoplasmic reticulum, and delivery into the lymphatic system. This same mechanism has reportedly applied to methoxychlor [26], another material soluble in lipids and lipid solvents. On the other hand, paraquat, a compound highly soluble in water (67 g in 100 ml), is usually highly ionized, with two positive charges per molecule. Accordingly, it is poorly absorbed from the intestinal tract [27].

(d) Ocular Exposure

The concentration of toxicant that contacts the exposed surface of the eyes due to spills or splashes may be greater than that reached in the body as a whole, so that local effects may be produced on the eye or its accessory structure (conjunctivae, eyelids, etc) in the absence of observable systemic effects. Upholt et al [28] discussed this phenomenon in a study of volunteers exposed to tetraethyl pyrophosphate in which no systemic illness was found, but in which miosis appeared.

Maddy and Topper [29] described many examples of eye injuries due to pesticides in California during 1975. One occurred to an employee who was working with a dust collector when some excess captafol powder was blown out causing the powder to enter through the side vents of his goggles, resulting in eye irritation. Another exposure occurred when a chemist observing a formulating procedure without wearing goggles was exposed to

chlorothalonil dust. He suffered from conjunctivitis and photophobia for 3 days and did not regain normal vision for a week [29].

General Toxicologic Effects of Pesticides

Pesticides have caused diverse toxic effects on various human and animal organs and organ systems including the liver, kidneys, skin, lungs, brain, nervous system, and eyes. Certain pesticides appear to be carcinogenic in humans and others have produced tumors of vital organs in test animals. They have also caused structural and functional defects in unborn experimental animals and mutagenic changes in hereditary characteristics in in vivo and in vitro test systems.

The many types of chemical compounds used as pesticides can be grouped on the basis of chemical structure into generic classes such as chlorinated hydrocarbons, OP's, carbamates, and chlorophenoxy acid esters and salts. While there are significant variations in the toxic effects of the individual pesticides within each structural class, common effects have been observed.

(a) Organochlorine Insecticides

DDT, aldrin, dieldrin, lindane, chlordane, toxaphene, and mirex are some of the most important OC pesticides in terms of production and use [7]. These compounds are all nonpolar substances and thus are soluble in lipids and organic solvents and are relatively resistant to metabolism or degradation. Consequently, these compounds have a strong tendency to penetrate cell membranes and to be stored in the body fat. Chronic,

long-term exposure to these compounds usually presents a more serious problem than acute exposure [30].

OC pesticides primarily tend to damage the liver and kidneys [2,31]. Several of these pesticides, including DDT [31], aldrin [2], dieldrin [2], and mirex [4,5], have produced benign and malignant tumors in the livers of chronically exposed experimental animals, particularly mice. The hazards from skin absorption are small when the material is dry or in powdered form. On the other hand, when dissolved in oil or organic solvents, the materials are well absorbed through the skin and constitute a considerable hazard. Behavioral changes, disturbances of sensory and equilibratory functions, involuntary activity of skeletal muscles, and depression of vital centers have also been attributed to exposure to OC insecticides, including DDT, aldrin, dieldrin, and Kepone [31-34].

(b) Organophosphorus Insecticides

There are a large number of OP insecticides in use. They include phosphates, phosphonates, phosphoramidates, pyrophosphates, thiopyrophosphates, and phosphorothioates.

In contrast to the OC insecticides, the OP compounds present a high hazard of acute intoxication which varies considerably from compound to compound. Parathion and fensulfothion are very toxic, with oral LD50's in rats of about 2 mg/kg [35]. Malathion is one of the least toxic compounds, with an oral LD50 in rats of 1,400 mg/kg [35]. These substances exert their toxic effects through their ability to inhibit cholinesterases (ChE's). OP compounds containing a P=S nucleus,

such as parathion, must be metabolically activated by exchanging an oxygen atom for the sulfur. Animals, man, and insects all perform this activation. In mammals, the activation is done by microsomal oxidases of the intestinal wall and liver. Other OP compounds do not require metabolic activation. The inhibition of ChE by active forms is essentially irreversible and renders their toxic actions persistent until the inhibited enzymes are replaced by newly produced ones. Repetition of a small dose may finally result in serious intoxication even though each single dose may inhibit only a small percent of the ChE activity. The symptoms result from the accumulation of excessive quantities of acetylcholine at peripheral, ganglionic, and central nerve endings and from an elevated concentration of acetylcholine in the blood plasma and interstitial fluids. Poisoning with reversible inhibitors, such as tetraethyl diphosphate (TEPP), is naturally more amenable to therapy.

Increased bronchial secretions, salivation, sweating, bradycardia, miosis, muscular weakness, hyperglycemia, low blood pressure, anxiety, headache, neurosis, slurred speech, disorientation, and convulsions are signs and symptoms that characterize poisoning by this group of compounds [36]. Respiratory failure is the most usual cause of death from a single, high dose. Such failure results from a combination of blockage of the respiratory tract from excessive secretion from glands of the mouth and respiratory tract, by possible bronchoconstriction, and by paralysis of the respiratory areas of the brain stem [37,38].

The degree of acute intoxication by most OP compounds may be gauged readily by the measurement of the extent of inhibition of acetylcholinesterase (AChE) in red blood cells (RBC's) or of the nonspecific ChE present in plasma. Axonal degeneration followed by degeneration of myelin sheath cells in peripheral nerves, and even in some cases, of degeneration of tracts within the spinal cord, has been observed. Such effects resulted from prolonged exposure to such OP compounds as tri-o-cresyl phosphate [39], mipafox [40], and leptophos [41]. Some evidence has accumulated that the chronic depression of AChE activity by OP compounds may be associated with behavioral changes [42-44], but there is some doubt of the scientific validity of these conclusions [45-47]. Based on analysis of available human and animal data pertaining to behavioral changes attributed to OP pesticides, it appears that insufficient criteria exist for assessing the significance of relatively subtle, apparently reversible, alterations in brain function on the health of exposed workers. However, there is cause for concern and additional research is recommended in this area.

(c) Carbamate Insecticides

These insecticides, which include carbaryl, methomyl, and propoxur, have more recently come into wide use. They are also ChE inhibitors and produce symptoms in humans similar to that of the OP insecticides. Unlike some OP compounds, the carbamates do not require activation by microsomal enzymes to inhibit ChE. The inhibition of ChE by carbamates is more readily reversible than that produced by most OP compounds [36]. Overexposure may result

in local effects, such as constriction of the pupil of the eye, sweating on a localized area of skin, secretion of fluid by glandular mucosa, etc. After absorption into the blood, the compound will contact first the ChE of the plasma and the erythrocytes and will inhibit one or both of them. Detoxification and dissociation of the inhibitor from the enzyme begins promptly, and the concentration of active enzyme in the blood rapidly assumes normal values while ChE in the central nervous system (CNS) or in effector organs may still be depressed. In this case, measurement of blood ChE activities would yield normal values and might lead the physician to conclude falsely that the patient had not been poisoned by a ChE inhibitor. Even though a blood sample may be taken at a time when its ChE activity is still depressed, dissociation of a carbamate inhibitor from the enzyme will proceed by hydrolysis after the blood sample has been collected. When carbamates are the compounds of interest, it is important that blood samples be examined for ChE activity as soon after collection as possible and that a rapid sampling and analytic method be used involving no, or minimal, dilution of the blood. However, due to the rapid reversal of carbamate-induced ChE inhibition, NIOSH does not recommend routine monitoring for persons exposed only to carbamate insecticides.

(d) Inorganic Arsenicals

Lead arsenate, Paris green, and sodium arsenite are insecticides that have been used for many years. Arsenic compounds are invariably dangerous cellular poisons [48]. They

exert their effects by reaction with sulfhydryl groups of important enzymes and are capable of affecting most organs in the body. Symptoms of acute intoxication include nausea, vomiting, diarrhea, intense pains or cramps in the intestine as well as in the stomach and esophagus, rapid fall of blood pressure to shock levels, convulsions, coma, and death. Symptoms and signs of chronic arsenic poisoning are characteristic gastrointestinal pains and diarrhea, injury and degeneration of the kidneys, edema, fatigue, and loss of appetite. Characteristic skin changes, which may appear also in mucous membranes, are flushing, edema, acne, and thickening and scaling of the epidermis. Hair loss, detachment of fingernails and toenails, and sometimes fatal exfoliative dermatitis may occur. Inorganic arsenic has been shown conclusively to produce skin cancer by prolonged use as a therapeutic agent [49]. Increased incidences of skin cancers, respiratory cancers, and leukemias have been observed in pesticide workers exposed to inorganic arsenicals [50].

(e) Nitrophenolic Herbicides

Nitrophenolic herbicides, such as the dinitrophenols and dinitro-o-cresol (DNOC), are highly toxic to humans and animals [36]. Most nitrophenols and nitrocresols are well absorbed from the gastrointestinal tract, through the skin, and from the lungs when very fine droplets are inhaled [36]. They irritate the skin and usually produce a yellow stain whenever contact occurs. Like other phenols, they are toxic to the liver, kidneys, and nervous system. The basic mechanism of toxicity is probably the uncoupling of oxidative phosphorylation [36]. Increased

oxidative metabolism depletes body carbohydrate and fat stores and leads to hyperpyrexia, tachycardia, and dehydration [36]. Symptoms of poisoning from these compounds are more severe when the ambient temperature is high [36]. Direct action on the brain causes cerebral edema which is manifested clinically as a toxic psychosis and sometimes as convulsions. Liver parenchyma and renal tubules show degenerative changes; albuminuria, pyuria, hematuria, and increased blood urea nitrogen (BUN) are often prominent signs of renal injury. Agranulocytosis has occurred following large doses of dinitrophenol [36]. Dinitrophenols have also been implicated in the formation of cataracts [51].

(f) Chlorophenoxy Herbicides

The chlorophenoxy acids, salts, and esters are irritating to skin, eyes, and respiratory and gastrointestinal linings. They are absorbed through the gut wall, the lung, and the skin. These acids are not significantly fat storable, and excretion occurs within hours or at the most within days, primarily in the urine [36]. They are regarded as being fairly nontoxic, although three cases of peripheral neuropathy were reported in workers after exposures to 2,4-D [52]. In a few individuals, local depigmentation has apparently resulted from prolonged and repeated dermal contact with these substances [36]. Some chlorophenoxy compounds have caused severe cases of dermatitis or chloracne in workers, although in some cases contaminants were the responsible agents [53].

Chlorinated dibenzodioxins (TCDD) are contaminants of 2,4,5-T. Neurotoxic effects and chloracne have been found in

workers exposed to TCDD-contaminated 2,4,5-T. Experimental animals exposed to TCDD may suffer teratogenic and mutagenic effects [54].

(g) Dipyridyls

Paraquat and diquat are the best known compounds of this class of herbicides. The dipyridyl compounds can bind to and injure the epithelial tissues of the skin, nails, eyes, nose, mouth, and respiratory and gastrointestinal tracts. Concentrated solutions cause inflammation and sometimes necrosis and ulceration of mucosal linings [36].

Autopsy cases of accidental or suicidal poisonings from paraquat show evidence of lung, liver, and kidney damage. Some cases had myocarditis, and one case showed transient neurologic signs. Most striking was the widespread cellular proliferation in the lungs [55]. Indications of diffuse toxic pneumonitis appear from 72 hours to 14 days after ingestion of paraquat. The pulmonary lesion has a complex histopathology, beginning with intra-alveolar edema and hemorrhage, followed by the proliferation of fibrous connective tissue. This fibrous connective tissue proliferation is often progressive and generalized and frequently results in death in 1-3 weeks [36].

(h) Urea, Uracil, and Triazine Herbicides

Monuron, bromacil, atrazine, and simazine are some of the better known herbicides in these categories. They have low oral acute LD50's, generally being above 1,000 mg/kg [55].

Most injuries reported with these herbicides involve skin irritation after prolonged contact. Some of these chemicals have

been implicated in injuries to the nervous system, liver, and kidneys, and have been known to cause increased permeability of capillaries at very high dosage levels in small laboratory animals, sheep, and cattle. Anemia and altered adrenal function have been detected in animals given extreme doses of atrazine [56]. These effects have not been observed in persons exposed occupationally or by accidental ingestion [36].

The herbicide amitrole, although not classified as a triazine, is structurally similar. This compound also has a very low acute oral toxicity in rats and mice, with a range from 15,000 to 25,000 mg/kg [55]. However, amitrole is a potent antithyroid agent, and significant effects on thyroid function have been observed at feeding levels as low as 2 ppm [57]. Amitrole has induced adenomas and adenocarcinomas in rats given 100 ppm in the diet for 2 years [58] and is also the chemical suspected of inducing an increased incidence of cancer in Swedish railway workers [59].

(i) Dithiocarbamates

There are three main groups in this class of fungicides. The first group contains the dimethyl derivatives including thiram, ziram, ferbam, and vapam. The second group is composed of the diethyl derivatives such as ethyl selenac, ethyl zimate, ethyl tellurac, and ethyl cadmate. And finally, there is the group of ethylene (bis) dithiocarbamate derivatives, which includes the pesticides zineb and maneb.

Many of the dimethyldithiocarbamate compounds are irritants and sensitizers [36]. The toxicity of these compounds

probably resembles that of disulfiram (Antabuse), which is used to condition individuals against beverage alcohol. They are metabolized in a manner similar to that of disulfiram. Disulfiram metabolites are powerful inhibitors of multiple sulfhydryl enzymes in the liver [60,61] and the CNS. Animal experiments indicate that thiram is more toxic than medicinal disulfiram [36]. Preliminary results reported by NIOSH [62] indicate that a serious toxic synergism exists between disulfiram and ethylene dibromide (EDB). In rats fed 0.05% disulfiram in the diet, mortality was 3/48 for males and 3/48 for females. Rats exposed to 20 ppm EDB by inhalation experienced mortality of 15/40 for males and 9/48 for females. However, rats exposed to both 0.05% disulfiram in the diet and 20 ppm EDB in air experienced mortality of 45/48 for males and 47/48 for females. All exposure periods were 13 months, and cause of death included an increased incidence of various tumors, including hemangiosarcomas of the liver, spleen, and kidney. Mortality for controls was 0/48 for males and 3/48 for females.

The toxic effects of these compounds can be categorized as those following absorption of the toxicant alone, and as those which result when the dithiocarbamate is followed by alcohol. Peripheral neuropathy and psychotic reactions have occurred in alcohol-abstinent individuals on high disulfiram regimens. Disulfiram followed by alcohol is characterized by flushing, excessive sweating, weakness, upper respiratory congestion, labored breathing, and in some cases, respiratory depression that has been life-threatening. High dietary intake of ferbam and

zineb has produced functional and anatomical damage to the CNS in rats [36].

In a screening study done by Bionetics for The National Cancer Institute (NCI) [4], a number of these pesticides were tested for their carcinogenic effects in mice. Elevated tumor incidences were observed in the mice fed ethyl selenac and bis (2-hydroxyethyl) dithiocarbamic acid potassium salt [4], whereas no significant increase in tumors was seen with zineb, maneb, ferbam, ethyl zimate, methyl zimate, methyl selenac, and ethyl cadmate. The authors also concluded that additional evaluation of ethyl tellurac and sodium diethyldithiocarbamate was needed. Ethylene thiourea (ETU) caused elevated tumor incidence when administered orally [4]. ETU is an oxidation product of the ethylene bisdithiocarbamate fungicides. Many compounds of this class, including zineb and maneb, are skin irritants and have caused dermatitis [63].

(j) Organomercurials

Organic mercury compounds are used as fungicides for seed, bulb, and corn treatment, and include phenyl mercury acetate, N-ethylmercuri-1,2,3,6-tetrahydro-3,6-endomethano-3,4,5,6,7,7-hexachlorophthalimide (EMMI), N-methylmercuri-1,2,3,6-tetrahydro-3,6-endomethano-3,4,5,6,7,7-hexachlorophthalimide (MEMMI), and 2-methoxyethylmercuric chloride.

Because these pesticides contain mercury, they should be regarded as highly dangerous. Compounds of mercury may be absorbed through the skin, the gastrointestinal tract, and the lungs. If high concentrations of ionizable mercury reach the

small intestine, severe abdominal pain and bloody diarrhea will result, with possible sudden death due to shock and circulatory collapse [64,65]. In general, the signs and symptoms of aryl and methoxyethyl mercury poisoning resemble those observed for inorganic mercury compounds [66]. Alkylmercury compounds also affect the nervous system, and the signs and symptoms include tremors, slurred speech, motor weakness, and abnormal reflexes [64]. The health effects of poisonings by mercurials are further described in NIOSH's criteria document on inorganic mercury compounds [67].

(k) Organotins

Trialkyl and triaryltin compounds are used as rodent repellants, molluscicides, fungicides, insecticides, and bactericides. Examples include triphenyltin acetate, bistributyltin oxide, tricyclohexyltin hydroxide, and triphenyltin hydroxide.

Adverse effects produced by occupational exposure to pesticide products containing triphenyltin acetate include irritation of the skin, conjunctivae, and respiratory tract, and liver damage. Signs and symptoms of poisoning by organotin compounds include general malaise, violent headaches, nausea, vomiting, diarrhea, and epigastric pains. These effects are described in detail in NIOSH's criteria document for organotin compounds [68].

(l) Miscellaneous Pesticides

Fumigants in common use include halogenated compounds such as methyl bromide and sulfuryl fluoride, cyanide compounds such

as acrylonitrile and hydrogen cyanide, and aluminum phosphide, a generator of phosphine. They are all highly toxic substances, especially by inhalation. They are intended for fumigation where there should be no exposure to humans. The halogenated aliphatic fumigants include liver, kidney, cardiac, and CNS intoxicants. Hydrogen cyanide is a rapidly acting poison which inhibits cytochrome oxidase, an enzyme necessary for the oxidative metabolism of all cells [36]. NIOSH has recommended that acrylonitrile be handled in the workplace as a suspect human carcinogen [69] and the Occupational Safety and Health Administration (OSHA) has regulated acrylonitrile as a carcinogen. This recommendation was based on data from animal experiments and on an epidemiologic study of workers handling acrylonitrile in a textile plant.

The coumarins and the indandiones are used as rodenticides. Warfarin is one of the best known coumarins [55]. These substances antagonize the action of Vitamin K to promote the hepatic production of prothrombin and several other clotting factors [55,70].

Another rodenticide of interest is 1-nitrophenyl-3(3-pyridylmethyl)-urea (Vacor). Unlike the coumarin-indandione rodenticides, Vacor has no anticoagulant action [36]; its exact mechanism of toxicity is unknown. Human poisonings have occurred only after deliberate ingestions, with varying symptoms depending on the dose and individual susceptibility. Ingestion is followed 4-48 hours later by nausea, vomiting, abdominal cramps, and mental confusion. These

may be followed by aching and tremors of the extremities, peripheral neuropathy, muscular weakness, and anorexia. Late and persistent manifestations of poisoning are postural hypotension and diabetes mellitus [36].

The fluoroacetates are another type of rodenticide. Sodium fluoroacetate is a powerful inhibitor of the tricarboxylic acid cycle and produces death by interfering with the operation of this important metabolic mechanism [36,55,71]. By forming fluorocitrate, it competitively and tightly occupies the receptive site of the enzyme aconitase and thus blocks the remainder of the tricarboxylic acid cycle [72]. It may cause cardiac ventricular fibrillation or convulsions, depending in large part on the species to which it is introduced. Sodium fluoroacetate is an extremely dangerous acute intoxicant.

Herbicides such as the acetanilides, acetamides, carbanilates, and anilides have recently been developed. These herbicides exhibit low systemic toxicity in laboratory animals, but irritate the skin, eyes, and mucous membranes. Propachlor and alachlor appear to have sensitizing properties; severe skin reactions have occurred in sensitive individuals [36].

Human Health Effects

While the United States has escaped major incidents of mass acute fatal poisoning, other countries have not [73]. Table XIV-6 lists the major cases of mass poisonings experienced throughout the world that clearly show the potential for great tragedy when pesticides are handled improperly. A variety of

toxic effects have been observed in workers exposed to pesticides during their manufacture and formulation. Workers who have been affected include formulators, mixers and loaders, cleaners and repairmen of pesticide handling machinery, warehouse workers, and truck loaders. The recent cases of occupational poisonings by Kepone, leptophos, and DBCP in the United States clearly demonstrate the variety of toxic effects that pesticides can manifest and the need for good engineering controls and work practices during the production and formulation of these pesticides.

In assessing how widespread this problem is in the workplace, the most reliable source of information comes from California. California's State Workmen's Compensation Law requires the reporting of injuries from occupational exposures. This requirement has led to the development of a statewide data base indicating the kinds and severity of injuries from pesticide exposure. In 1973, a total of 1,451 cases of occupational disease attributed to pesticides and agricultural chemicals was reported in California [17]. Of these, 156 occurred in manufacturing establishments. The breakdown of these cases by class of compound, specific agent, and industry category is shown in Table XIV-7. There were 1,343 reported occupational illnesses resulting from exposures to pesticides in California in 1975 [74]. Of these, 546 were concluded to be systemic, 436 involved skin injuries, 314 involved eye injuries, and 47 involved both the skin and the eyes. Fifty-four of the 1,343 cases involved pesticide manufacturing and formulating workers [29]. Of these

54 cases, 39 had systemic effects, 5 involved skin effects, 8 had eye changes, and 2 involved eye and skin injuries. The pesticide mevinphos was responsible for 25 of the 39 systemic illnesses. Other pesticides believed to have caused injuries include parathion, methomyl, penoxalin, chloropicrin, carbaryl, captafol, and malathion.

While statistical data on injuries and illnesses from occupational exposures to pesticides are available from California, similar data are not available on a national basis. Unavailability of these data has limited attempts to characterize the potential danger of individual pesticides and to identify those pesticides which present a higher risk to workers due to toxicologic properties and to overexposure because of poor work practices and controls. Accordingly, NIOSH has published a guideline for reporting occupational disease [75] which, if implemented, would provide better data on occupational health problems, including those associated with pesticides, than are currently available.

Much of the information now available on the human toxicity of pesticides comes from reports of accidental or suicidal exposures. They provide valuable accounts of the types of effects which result from pesticide exposure. In addition to case reports, some epidemiologic studies have been reported that provide information on the effects of chronic exposures in workers handling pesticides. Review of case reports and epidemiologic studies reveals the variety of effects which are seen as a result of pesticide exposure. Human exposures to

pesticides affected the skin, eyes, and nervous, reproductive, hepatic, renal, respiratory, hematopoietic, and cardiovascular systems. Moreover, available studies have implicated the inorganic arsenical pesticides [48,50,76], benzene [77-80], acrylonitrile [69,81], creosote [82], certain hexavalent chromium salts [83], and amitrole [59] as human carcinogens. The following discussion of human health effects is arranged according to the different target organs.

(a) Neurologic Effects

Neurotoxicity is a well-documented toxic effect of pesticides in humans, often in association with the OP, carbamate, and OC pesticides [55]. Two major incidents of occupational neurotoxicity associated with pesticides involve the OC pesticide Kepone and OP pesticide leptophos.

Kepone is a chlorinated hydrocarbon insecticide used domestically as an ant and roach poison. It is related to the pesticides mirex, DDT, aldrin, and dieldrin, all of which have been restricted by the EPA. Kepone was produced in Hopewell, Virginia, in a converted garage which began operation in 1973; the plant produced only Kepone [34,84].

In July 1975, a Hopewell physician submitted an employee's blood sample for analysis to the Center for Disease Control in Atlanta. The analysis revealed a Kepone blood level of 7.5 ppm (CW Heath, Jr, written communication, January 1976). Subsequently, workers at the Hopewell plant were discovered to have a variety of ailments which led to a detailed study and investigation of 133 employees out of the total of 148 then

current and previous employees [34].

The workers suffered complex neurologic disorders characterized by insidious onset of tremors, chest pains, weight loss, mental changes, arthralgia, skin rash, opsoclonia, muscle weakness, loss of coordination, and slurred speech. Seventy-six of the 133 (57%) had experienced tremors following exposure to Kepone. The findings indicated that Kepone produces neurologic disorders involving the brain, the peripheral nerves and muscles, and the liver [34]. In addition to the neurologic findings, sperm counts showed cligospermia with no motile forms (CW Heath, Jr, written communication, January 1976). NCI has released the results of a study indicating that Kepone is carcinogenic in the mouse and the rat [85].

The testimony and photographs submitted at the Senate Hearings of April 21, 1976 [84] show that not even minimal health standards were applied at the Hopewell plant. Kepone exposure was not in the least controlled, and extremely poor housekeeping practices existed at the plant. Consequently, workers were exposed to the massive amounts of Kepone that led to the reported intoxications.

A recent study [86] has indicated that cholestyramine shows promise as a detoxification agent for workers exposed to Kepone. In 22 Kepone-exposed workers administered 16 grams of cholestyramine per day for 5 months, mean blood half-life of kepone was reduced from 165 to 80 days and the mean fat half-life was reduced from 125 to 64 days.

Another dramatic example of occupational poisoning

involved leptophos, an OP insecticide. Leptophos was produced in Texas for export until January 1976. In June 1975, 12 cases of serious neurologic disorders in employees were identified by a medical consultant to the manufacturer. These cases were not reported to NIOSH until September 1976 [87].

Following notification of the neurologic disorders in September 1976, NIOSH began a study in December 1976 of all present and former employees. NIOSH contacted the majority of the 301 then current and former employees and informed them of the availability of medical examinations. Between January and April 1977, 155 persons reported for comprehensive examinations that evaluated general physical status, neurological status, and measures of neuromuscular, ophthalmological, psychological, and biochemical function. A reproductive history survey was also conducted [41].

A substantial number of those examined had slight to serious neurologic, electromyographic(EMG), electroneurographic (ENG), and psychologic performance abnormalities. Many of those studied showed sensation abnormalities of the hands and feet. Results of the psychologic performance tests for those exposed, when compared with the results for unexposed controls, suggested an impairment of psychomotor performance. A few of those studied showed significant EMG abnormalities. Most of the abnormalities involved three muscles: the extensor digitorum brevis, abductor hallucis, and gastrocnemius. Fifty-seven workers had abnormal ENG results. Out-of-range latency measurements for the sensory nerves (median, ulnar, and sural) were found for 17, 13, and 7%

of the participants, respectively. Of the 29 workers with abnormal latency findings, 8 showed abnormal findings for both the median and ulnar nerves. The number of out-of-range values for muscle action potentials and nerve conduction velocities of motor nerves was greater than expected. Results from chest X-ray and blood and urine tests revealed no unusual findings. No statistically significant differences were found in the reproductive history survey [41].

NIOSH medical officers believe that the signs seen in these workers are compatible with OP poisoning, even though a number of other chemicals were used in the manufacture of leptophos including toluene, a suspected neurotoxic solvent. Also, during the period of 1971-75, the plant also manufactured a resin called Klyrvel which required use of n-hexane, a solvent that has been associated with severe neurologic disorders [41]. NICSH concluded that the health of the workers involved was adversely affected by conditions that could have been prevented by more careful medical surveillance, work practices, and engineering controls.

The incidents with Kepone and leptophos directed national attention to the hazards of pesticide exposure in manufacturing and formulating workplaces, and to the problem of occupational neurotoxicity. The literature reveals many other reports of neurotoxic effects by pesticides, and some of these reports are presented in the following paragraphs, according to chemical composition.

(1) Organophosphorus Insecticides

The neurologic effects resulting from exposure to OP insecticides can be classified as effects either directly related to ChE inhibition or delayed neurotoxic actions.

(A) Cholinesterase-Mediated Effects

Most OP poisonings involve effects that are directly related to ChE inhibition. The mechanism of toxicity involves the inhibition of AChE at cholinergic nerve synapses with resulting accumulation of acetylcholine at these sites. This leads initially to junctional transmission and later to inhibition of synaptic transmission as the postjunctional membrane develops a state of persistent depolarization [37]. A more detailed discussion of the mechanism of ChE inhibition is provided in the NIOSH criteria documents and recommended standards for the OP insecticides malathion [88], parathion [89], and methyl parathion [90].

Most poisonings involving ChE inhibition result from acute exposures. Due to their rapid metabolism and excretion, accumulation of OP insecticides in the body does not occur [55]. Small repeated exposures, however, can result in progressive inhibition of ChE which, if it continues, can reach a level at which signs and symptoms will occur similar to those produced by a single high dose. The manifestations of poisoning resulting from accumulated acetylcholine in nerve tissue and effector organs can be classified as muscarinic, nicotinic, and CNS effects. Muscarinic effects involve smooth muscle, the heart, and exocrine glands. They include respiratory tightness, sweating, nausea, vomiting, abdominal cramps, and pupil

constriction (miosis). The nicotinic effects involve muscular fatigue and weakness, twitching, fasciculations, and cramps. The CNS effects include tension, anxiety, headache, emotional instability, confusion, ataxia, slurred speech, convulsions, and respiratory and circulatory depression [55,37].

The onset of these systemic effects varies with the compound, the route, and the degree of exposure. According to Vale and Scott [37], the interval between exposure and symptoms may be as short as a few minutes, is usually less than 12 hours, and rarely exceeds 24 hours. In most cases, unless exposure causes death, neurologic effects dependent upon inhibition of ChE's are reversible. Local and less severe effects usually last less than a day. Miosis often disappears in less than a week, and most other symptoms diminish over the next 6 to 18 days [91].

Diagnosis of OP poisoning is usually based upon symptomatology and blood ChE levels [92]. Although symptoms are not directly related to blood enzyme activities, the activity of the enzymes in the blood usually provides a rough approximation of the activity in the nervous system [92,93]. Measurements of blood ChE levels are therefore a useful indication of the extent of poisoning. The following case studies present an overview of the signs and symptoms seen in OP acute poisonings.

Vale and Scott [37] reported an OP pesticide poisoning in a 51-year-old female formulation worker. The woman was exposed to demeton-S-methyl while repackaging it in a poorly ventilated room. She first noticed that her pupils were very small, while combing her hair during the afternoon break. Within a few

minutes she had a violent abdominal cramp, vomited, sweated profusely, developed severe diarrhea, and fainted. The woman was hospitalized and developed characteristic nicotinic twitching of abdominal and limb muscles. Following treatment with atropine and diazepam, her condition improved and her RBC ChE activity returned to its preexposure level within 10 weeks.

Grigorowa [94] investigated poisonings in a German plant producing methyl parathion. The first series of examinations, in February of 1959, involved 47 workers. Of the 47 studied, 18 (39.3%) reported mild symptoms, including lack of appetite, gastric distress, visual disturbances, sleeplessness, fatigue, nervousness, and slight headaches. Severity of the symptoms did not appear to be related to length of employment, which ranged from a few months to 6 years. Although plasma ChE activity was apparently measured, no values were reported. The following July, 35 workers were examined and 29 reported more severe symptoms than those reported in February. The author stated that signs and symptoms indicative of CNS involvement were freguent and included headaches, dizziness, nausea, insomnia, fatigue, visual disturbances, increased perspiration, shooting pains in the heart, loss of appetite, vomiting, stomach pains, fibrillar muscular twitching of the eyelids, and numbness of the legs, arms, or fingers. Time of onset for these specific symptoms was not provided. Of the 29 symptomatic workers, 27 had plasma ChE activities that showed activity inhibition of 11-68.4% compared with the February measurements. In 21 workers this inhibition was greater than 30%. It is not clear from the article whether

all of the 35 workers examined in July were members of the group of 47 workers examined in February.

The author included a brief description of two cases of poisoning seen in the plant during the summer of 1959. One case involved a 48-year-old worker with 5 years' work experience. The man developed a headache and became weak and dizzy while filling bags with methyl parathion dust. He lost consciousness for a few minutes at home after work. Identical symptoms recurred when work was resumed. He reported that his left hand had been numb for a few days, that his right hand had little feeling, and that he had experienced frequent twitching of the eyelids. When examined in February, he had complained of insomnia. When measured in the summer, plasma ChE activity was 64.4% of the February value.

Another case involved a 27-year-old worker with 1 year's experience. He had no complaints during the February examination, but when examined in July, he complained of severe headaches, loss of appetite, nausea, watering of the eyes, and insomnia. For 8 weeks, he had experienced arm and leg numbness with arm impairment sometimes involving only two or three fingers. In the July examination, his plasma ChE activity was 60.2% of the February value.

Petty [95] reported two cases of OP insecticide poisoning. The first involved an employee of an agricultural experiment station who participated for three spring seasons in spraying trees and plants with various pesticides, including parathion, EPN, DDT, dieldrin, and lead arsenate. He did not handle

pesticides during the fall and winter months. The first two springs the patient experienced symptoms of nausea, cramping, aches, and pains which decreased during the fall and winter. During the third spring he noted symptoms similar to those he experienced previously along with nervousness, and difficulty in balancing. Eventually he was found unconscious and was hospitalized, where he was weak, lacked sensation in the hands and feet, and had paresthesias of the extremities. Plasma and RBC ChE's were 34 and 37% of normal, respectively. Although blood ChE activities returned to normal, his symptoms persisted with varying severity during the next 2 years.

The second case involved a physician who applied insecticides to his lawn and shrubbery every Sunday. Initially he used DDT and other insecticides, but later used malathion exclusively. He sprayed a 6% malathion solution with a garden hose attachment and was often thoroughly soaked with spray after the application. After several months of such spraying, he was tired, irritable and experienced paresthesias of the face and oral cavity. The next spring, soon after applying a 50% malathion solution to plants in his yard and living room, he experienced marked weakness, tremors, and headaches. He collapsed and was hospitalized. During his hospital stay he improved, but facial sensation was still decreased, gait was unsteady, and muscles were weak. The following year the patient was still experiencing marked muscle weakness, fatigue, and loss of appetite.

Both individuals included in this study had repeated

exposures to various pesticides. Although depression of blood ChE levels was measured in the first man, no such evidence was available for the other individual. The author does mention that there may be no relationship between the OP exposure and the peripheral or cranial nerve damage.

Low doses of OP insecticides are thought to depress ChE activity without causing the symptoms of acute poisoning [90]. In such asymptomatic individuals, determination of subclinical alterations was made by measurement of blood ChE's, by electromyography, and by electroencephalography.

The literature reveals differing opinions on the most sensitive means for determining the effects of subclinical exposure to pesticides [96,97]. In a study of 36 workers exposed to OC and OP pesticides at a Dutch chemical company [96], 16 workers were tested and found to have an abnormal electromyogram. These EMG responses were quantified by measuring the maximal voltage of the muscle action potentials elicited by optimal stimulation of the motor nerve to the adductor pollicis muscle in the forearm. Abnormal EMG responses were often observed, although blood ChE activity levels were normal. This was observed often in workers whose primary exposure was to OP and carbamate compounds and rarely in workers who mainly handled CC pesticides. The authors stated that measurements of blood ChE levels can be misleading in determination of overexposure to many compounds, especially when the exposure is of a chronic nature. They suggested observation of subjective symptoms, such as headache and nausea, or EMG recording, as preferred indices of

overexposure in pesticide workers.

Jager et al [97] also used EMG's to study workers engaged in the manufacture and formulation of OP and OC pesticides. The OP compounds involved were dimethyl vinylphosphates; the OC compounds were unspecified. EMG and whole blood ChE activity were measured. Of the 36 workers exposed to OP pesticides, 17 had abnormal EMG readings compared with only 1 abnormal EMG reading in 28 workers exposed only to OC pesticides. The abnormal EMG's of pesticide workers were similar to the EMG's of the patients with myasthenia gravis, a condition characterized by muscle weakness and fatigability. The difference between the EMG patterns of healthy individuals and myasthenic patients is that the action potential spikes in a train have about the same amplitudes in normal subjects, whereas in myasthenic patients the action potential spikes, after the first discharge in a train, decrease in voltage progressively and rapidly. In pesticide workers, signs of progressive impairment of EMG appeared over a workweek and then disappeared over the weekend. The researchers did not find, however, a correlation between abnormal EMG readings and depression of the activity of ChE's in whole blood.

Other means have been employed to detect effects of OP pesticide exposure. Rayner et al [98] suggested that hyporeflexia may be a sensitive indicator of chronic OP pesticide exposure. They studied Japanese orchid farmers selected on the basis of high OP usage. They were also exposed to fungicides and OC's. The force of the Achilles tendon reflex was measured objectively with a machine designed for that purpose and showed a

depression of the reflex as compared with controls (P=0.001) and confirmed preliminary observations of hyporeflexia in the exposed agricultural workers. At the present time no completely satisfactory criteria exist for determining the significance of slight alterations in brain electrical activity, as determined by electroencephalography, or in neuromuscular function, as determined by electromyography, on the health of exposed workers.

(B) Delayed Neurotoxic Effects

Delayed neurotoxic effects have also been attributed to the OP insecticides. While substantial data are available on delayed neurotoxic effects in experimental animals from exposure to pesticides [99-101], few human cases have been reported. It has been suggested that delayed neurotoxicity is the result of some action other than ChE inhibition, such as axon degeneration followed by demyelination of tracts in the spinal cord or of peripheral nerves [39]. Demyelination was the probable explanation for the paralyses seen in "Ginger Jake" poisoning caused by tri-o-cresylphosphate (TOCP) [39,102]. Such effects have been reported also for the OP pesticides, mipafox [40] and leptophos [41].

Bidstrup et al [40] reported three cases of delayed paralysis in research chemists involved in the production of mipafox. These individuals had previously experienced symptoms of mild poisoning while exposed to other OP compounds. In the first case, the initial signs and symptoms were vomiting, muscular weakness, and eye problems. Following treatment for her acute poisoning, the patient was released. Three weeks later the

patient was rehospitalized with flaccid paralysis of both legs. The muscles of the right hand were also weakened, and paralysis progressed over the next few weeks. During this time, blood ChE activity levels were greatly reduced. Cranial nerves were normal. EMG studies showed reduced interference patterns. All muscles were tender, and twitchings of leg and face muscles occurred. The patient's condition improved slowly, although leg muscles below the knee remained paralyzed. Six months later the patient was still in a wheelchair, although toe and ankle movements were increasing. Nine months after initial exposure to mipafox, EMG's showed evidence of a lower motor neuron lesion. This patient was able to leave the hospital after about 2 years, but still has, some 26 years after the incident, weak leg muscles so that walking is difficult and must be assisted by a cane or other supporting device (JH Wills, written communication, May 1978).

A coworker of case one initially experienced respiratory difficulties and eye irritation. A week and a half later the patient experienced weakness and loss of tone in the muscles of both lower limbs, particularly below the knee. An EMG showed a reduced interference pattern but no sign of lower-motor neuron degeneration. The patient's condition improved gradually, but after discharge, he had bilateral foot drop, which was more pronounced on the right side. Six months later the patient still experienced tiredness, and after walking 200-300 yards, his foot became "floppy."

The third affected worker was much less severely poisoned

than the other two and never required hospitalization. The authors [40] believed that in the two most severely affected cases, prolonged failure of impulse transmission at the motor end-plate initially contributed to the paralysis. However, subsequent EMG's in case one were indicative of peripheral neuritis with no evidence of neuromuscular block. For that reason the authors felt that demyelination was the most likely cause of the persistent symptoms.

(2) Carbamates

The carbamate insecticides are also ChE inhibitors [17] and the symptomatology in affected humans is similar to that produced by OP insecticides. However, inhibition of ChE's by carbamates is readily reversible [17].

Cases involving methomyl include a mill operator and two laborers in a methomyl formulating plant who experienced episodes of acute intoxication within a 2-week exposure period. A foreman in another formulating plant reported being nauseated, dizzy, and feeling "drunk" after working with methomyl. In another case, a 17-year-old farm laborer who applied methomyl to an orange grove became ill shortly after work, lost consciousness, and was hospitalized for 1 day. The adverse effects associated with methomyl included nausea, vomiting, dizziness, weakness, and respiratory abnormalities [17].

A case of poisoning by aldicarb involved the foreman of a manufacturing plant who ran a mechanical bagging machine for 1 day. Several hours after exposure, the foreman experienced nausea, dizziness, depression, weakness, and tightening of chest

muscles. RBC ChE was inhibited to 43% of normal. Three hours after the initial ChE measurement, the RBC ChE level was again measured and showed recovery; however, the individual still complained of tightness of the chest. By the next day he had recovered, and returned to work [103].

Tobin [104] reported on the anti-cholinesterase effects following exposure to carbofuran. A survey of workers in a carbofuran manufacturing plant revealed the following symptoms in decreasing frequency: vague feelings of malaise, excessive sweating, lightheadedness, nausea, blurring of vision, hypersalivation, and vomiting. No one reported chest tightness, muscular twitching, convulsion, or loss of consciousness. The author included two case studies which involved formulation workers who used a power concrete mixer to prepare a 10% granular product of carbofuran and complained of profuse perspiration, weakness, nausea, and blurred vision. One worker completely recovered 2 hours after exposure ceased, the other felt weak and nauseated 1 hour after exposure ceased but required no treatment.

A study of possible effects on CNS function after subchronic exposure to the insecticide carbaryl was performed by Wills et al [105]. For this study, male volunteers between 25 and 57 years of age were selected from inmates of a New York State prison. The carbaryl was administered orally in gelatin capsules. Dose regimens included: no dose, 0.06 mg/kg/day carbaryl for 6 weeks, and 0.12 mg/kg/day carbaryl also for 6 weeks. Indications of possible carbaryl-related subjective neurologic effects were found in interviews of the subjects

during and after the 6-week period of the study. Despite the apparent dose-relatedness of these neurologic symptoms, no decrease in blood ChE activity levels was seen except for a very slight depression observed in one individual in the low-dose group on day 3 of the test. Most of the subjective symptoms reported by the high-dose group did not appear until the 4th or 6th week of the study.

(3) Organochlorine Pesticides

While neurotoxic effects of OP and carbamate pesticides are fairly well documented, less information is available for other pesticide classes. In addition to Kepone, other OC pesticides have been associated with human neurotoxicity [32,33,106-110]. Although the precise mechanism of their neurotoxicity is unknown, the action of OC pesticides does differ from that of the OP and carbamate compounds [55].

Kazantzis et al [106] reported on a formulating plant worker who developed epileptiform convulsions after a short period of heavy exposure to aldrin. The man had been working with aldrin for little more than a week. His job was to transport paper bags of aldrin and fuller's earth (an inert filler), open the bags, and then empty them by hand into a mechanical mixer. He had to lean over into the exhaust hood of the mixer to do this. He wore overalls and a cotton wool pad as a mask. He had two convulsive attacks with loss of consciousness. Analysis indicated a high body fat concentration of dieldrin, the principal metabolite of aldrin. Electroencephalograms (EEG's) showed irregular alpha rhythms.

Later, nine fellow workers were also examined. Two of these nine workers described symptoms characteristic of aldrin poisoning. The two men worked on the micronizer and both experienced involuntary jerking of the limbs, irritability, and vomiting. EEG's revealed irregular alpha rhythms. Improvement was seen in both men following cessation of exposure. One of these men returned to work and subseguently experienced several attacks of unconsciousness. Blood and fat analyses showed high dieldrin content. Another worker, who was not among those previously examined, also lost consciousness and convulsed while working with the 50% aldrin mixture. An EEG contained abnormalities similar to those of the other three men with aldrin intoxication.

Nelson [107] reported convulsions in 3 of 35 workers exposed to 25% aldrin concentrate. The workers also complained of nausea, vomiting, vertigo, loss of weight, malaise, and headache; recovery in all cases was complete.

Bell [108] reported the case of a man overexposed to aldrin while repackaging 5-pound bags of the substance. Ventilation during this work was poor, and no attempt was made to prevent skin contamination. On the evening of the 2nd day of working under these conditions he had a convulsive seizure. An EEG examination revealed abnormalities, and a biopsy of fat 2 weeks later revealed 40 ppm dieldrin; the patient recovered fully.

Avar and Czegledi-Janko [109] studied 15 men exposed to aldrin in a fertilizer plant for varying periods of up to 5 years. The men were examined during the last month of their exposure. In three men with poisoning symptoms, EEG's contained

changes typical of convulsive states, and all had had convulsive fits. Blood dieldrin concentrations for these three individuals ranged between 0.3 to 0.19 ppm. Seven months after the last known exposure, both EEG findings and dieldrin concentration returned to background level, and clinical symptoms ceased. In others examined during the last month of exposure, signs and symptoms of poisoning were present when the concentration of blood dieldrin was greater than 0.10 ppm and were absent when it was less than 0.05 ppm.

Hoogendam et al [32,33] reported on a 9-year health survey of 300 workers in plants manufacturing OC pesticides. The pesticides involved were aldrin, dieldrin, and endrin. Although during that period no fatalities or permanent injuries were found, 17 of the workers experienced convulsive intoxications. Of these, 5 had more than one convulsion, and 2 had more than one convulsion on a single day. In several of the cases, convulsions were preceded by myoclonic jerks [32], but usually without any prodromal symptoms. Specific EEG anomalies including bilateral synchronous spike and wave complexes thought to be associated with alterations in brain stem function were observed [33]. Clinical and neurologic recovery after removal from exposure was rapid and complete in all cases.

Derbes et al [110] reported the case of a 23-year-old woman with 2 years' experience working in a pesticide factory who spilled an unknown amount of a suspension containing 25% chlordane, 26% DDT, 39% Velsicol AR 50, and 10% triton-X on the front of her clothing. Forty minutes later she became confused

and rather suddenly began having generalized seizures. She died in the ambulance on the way to a doctor's office suggesting massive exposure. Autopsy revealed nonspecific pathologic changes in the brain, lungs, and kidneys.

(4) Other Pesticides

Neurologic effects have been reported following exposure to a variety of other pesticides including methyl bromide [111,112], 2,4,5-T [53], monosodium acid methane arsenate [113], organomercury compounds [114], and diphenyl [115]. Greenberg [111] observed CNS damage in a worker who had been exposed to methyl bromide while fumigating cocoa beans. The worker first lost and then regained the ability to walk. Two months later, however, he suffered a recurrence of toxic manifestations with violent seizures and altered brain electrical conductivity, as shown by electroencephalography. Three years later the EEG pattern had improved, but there was still some lack of muscular coordination, and intelligence and personality tests showed that he was at the borderline of mental retardation. He appeared to have suffered mild to moderate permanent brain damage.

Hine [112] reviewed 10 cases of methyl bromide poisoning, 5 of which are discussed below. The review included three case reports of fatal poisoning. The first involved a worker who ate his lunch in an area adjacent to a boxcar full of rice which had been fumigated with methyl bromide the night before. That evening he developed sudden tonic-clonic seizures and lost consciousness. His wife drove him to the emergency room of a

hospital where he was given resuscitative measures. Upon examination he showed tremors, fasciculation of the muscles, cyanosis, and irregular gasping respirations. He died 20 minutes after the initial seizure. The second case involved a man who had fumigated almonds on the night prior to becoming ill. Four hours after leaving work he experienced difficulty in breathing, chest pain, chills, and excessive sweating. He was discovered later undergoing tonic-clonic convulsions and did not regain consciousness before death.

Poisoning was also seen in a man who worked up to 10 hours/day sacking rice, hauling it out of box cars, and piling it in a warehouse. He was unaware that the rice had been fumigated with methyl bromide in the car. He became ill on day 4 and his initial signs and symptoms included a cough and a sore chest. Six days later he had general muscular discomfort, mild disorientation, and difficulty in breathing. He was hospitalized and later died.

Hine [112] also reviewed two cases of nonfatal methyl bromide poisoning. One case involved a woman employed on an almond-sorting belt for 2 months. Fumigation was done in a warehouse 50 feet from her work station. The door to the warehose was open allowing the fumigant to drift down the conveyor belt. No fumigation had been done 48 hours prior to the pericd of her first reported illness. Her first symptoms were coolness of the chest and burning of the nose and throat. A second exposure occurred the following night after she had been at work 2 hours. She became ill and was unable to move her arms.

The next day she was confused, had headaches, nausea, and loss of leg control. She was hospitalized and began to hallucinate. Six months later she still had hallucinations, headaches, limb discomfort, and general body soreness. Laboratory examination showed persistent leukopenia and a moderately abnormal EMG. Thirty months after the initial symptoms, the patient was still not at work due to malaise, decreased reaction time, muscle pains, and depression.

Another man became ill within 1 week after he had cleaned dead worms out of a series of rooms that had been fumigated with methyl bromide 10 days earlier. The five rooms cleaned were 100 sq ft in size with small doors, no windows, and no permanent exhaust systems; however, air hoses had been rigged in an attempt to remove vapors. He worked inside the rooms about half a day for 4 days, did not wear a mask while working, and was not advised of the hazard. The man's first symptom was extreme nausea. He was taken to a hospital, where he lost consciousness for 4 hours. After regaining consciousness, his symptoms included nausea, weakness, numbness, dizziness, paranoia, and disorientation which persisted for 24 hours. No objective evidence of neurologic disease was found.

Other neurotoxins associated with pesticides are the chlorinated dibenzodioxins (especially 2,3,7,8-tetrachloro-dibenzo-p-dioxin, TCDD) that contaminate several pesticides, including the herbicide 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), the wood preservative pentachlorophenol (PCP), and the bactericide hexachlorophene. Jirasek et al [53] reported

TCDD-related neuropathy among factory workers in Czechoslovakia producing 2,4,5-T and PCP. The majority of 55 workers suffered what were stated to be severe neurasthenia and depressive syndrome. In 17 subjects, signs of peripheral neuropathy, especially in the lower extremities, were confirmed by electromyographic examinations.

De Palma [113] cited three cases of arsine intoxication in a chemical plant where monosodium acid methane arsenate (MSMA) was being produced. Two of the cases apparently involving the nervous system are described below. During the reaction of methyl chloride with sodium arsenite, a paddle became detached in the vat and the operation was stopped before completion of the reaction. The tank was drained, but a solid residue remained on the vat floor. An aluminum ladder was used to descend into the tank. The first man entered the tank without a mask or respirator to assess the damage. After a minute or two, he noticed bubbling at the foot of the ladder and bent over to get a closer look. He felt a sudden chill and left the vat. He soon experienced a burning sensation in his feet, which later involved his whole body. He then experienced nausea, vomiting, and abdominal pains. He was anuric, irritable, confused, and agitated when finally hospitalized. He was released after 54 days with pain, numbness, burning and hypoesthesia of his feet, ankle and leg weakness, and occasional finger numbness. The peripheral neuropathy was decreased, but still persisted 6 months later.

Another worker went halfway down the ladder and proceeded

to wash down the tank floor with a hose while steam was piped up through the center drain. He was in contact with rising steam for about 15 minutes. Shortly after this task he noticed that his urine was unusually dark. He became jaundiced and was hospitalized. During this period he experienced fever, paranoid delusions, anemia, and progressive weakness; he lost 50 pounds and could not walk more than 20 feet without having to rest. A program of physical rehabilitation was initiated. His condition improved and he was discharged. Six months later he still had partial loss of sensation on both feet and neuralgia in his toes and heels.

Ahlmark [114] documented five cases of neurotoxicity from methylmercury compounds in occupationally exposed individuals. The first case involved a man employed for 3.5 years in a factory where methylmercury was manufactured. He was specifically occupied with the extraction of methylmercury iodide and also with releasing the excess pressure in the bottles in which the methylmercury iodide had formed. The author noted that the man was known to be extremely careful in his work and that he observed all the protective precautions in detail. His first symptoms included giddiness, a "funny" feeling in his fingers, and numbness of the fingertips. These symptoms were followed by indistinct speech, numbness of the tongue, and trembling hands. His condition continued to deteriorate until he could not stand and his speech was barely understandable. After about 4 months he began to improve, but 9 months later he still suffered from muscular incoordination and could not eat properly.

Three of the five cases involved packers of seed dressings containing methylmercury. All experienced tingling in the hands. One of the cases progressed until the individual had difficulty walking, balancing, and speaking. The first individual died; the other two individuals had no other symptoms of poisoning.

The fifth case involved a man who had impregnated wood with methylmercury. His first symptoms included numbness in his hands and forearms, incoordination, dizziness, and an unsteady walk. The symptoms gradually increased, his speech was impaired, and he became blind. He died less than 1 month after hospitalization.

Seppalainen and Hakkinen [115] described a neurophysiologic study of 24 out of 31 workers exposed to the fungicide diphenyl in a Finnish paper mill where wrapping paper was impregnated with the diphenyl. The group included those exposed to the greatest amounts and/or who had symptoms or signs suggestive of poisoning, including headaches, gastroinestinal complaints, general fatigue and numbness, and aching of the limbs. Ten of the 24 workers had abnormal EEG's with mainly diffuse, slow wave abnormalities. During a 2-year observation period no actual improvement was seen. Some workers also had electroneuromyography (ENMG) abnormalities and 7 also exhibited fibrillations in some muscles. In addition, nerve conduction velocity, especially that of slower motor fibers, was reduced in several cases. The author did note that exposure to diphenyl highly exceeded the TLV of 1 mg/cu m, though no quantitative results were reported.

(b) Behavioral Effects

Neurotoxic responses to pesticides may also be manifested

as behavioral or psychologic alterations [43,44,116,117]. Such manifestations are often subtle and difficult to measure.

The behavioral effects of chronic but clinically nontoxic exposure to OP pesticides were reported by Korsak and Sato [43]. Thirty-two individuals were divided into two groups of low and high chronic occupational exposure based on a logarithmic index derived from yearly and daily exposure combined with age. The volunteers were tested using a series of neuropsychologic tests and a computer-based electroencephalographic technique. Blood was drawn for pesticide residue analysis and for plasma ChE activity determinations. The results indicated that extent of chronic exposure does have definite quantifiable effects upon apparently asymptomatic individuals. Length of exposure to high levels of OP pesticides was significantly related to deficits in performance on Part B of the Trial Making Test and on the Bender Visual Motor Gestalt Test. Both tests have been reported to be indicators of brain dysfunction. However, insufficient criteria exist to permit correlation of subtle, reversible alterations in brain function with the health of the worker. There were no significant relationships between length of exposure and deficits in performance on the Tactual Performance Tests.

Metcalf and Holmes [116] used EEG techniques, psychiatric interviews, visual and auditory evoked response tests, and physical examinations to measure response to pesticides. They found more cases of nervousness, changes in memory and sexual activity, problems in sleeping, and easy fatigability in persons exposed to OP pesticides than in the control group.

Dille and Smith [117] reported that two pilots employed in spraying OP pesticides suffered acute poisoning symptoms and later showed symptoms of severe depression and anxiety. The abnormal EEG of one pilot persisted for 6 months. The authors attributed the psychiatric symptoms to the effects of chronic exposure to OP pesticides.

Gershon and Shaw [44] discussed the psychiatric sequelae seen in four workers following chronic exposure to OP insecticides. The individuals involved were a scientific field officer employed in checking the efficacy of OP insecticides, including parathion and malathion, a greenhouse technician exposed to parathion, malathion, and other pesticides, a horticultural technical officer exposed during spraying of an unspecified pesticide, and a farmer exposed to malathion and other insecticides. Each had experienced symptoms of acute OP poisoning at various times prior to the detection of psychologic alterations. Depressive and schizophrenic reactions were observed in the four individuals. The authors [44] hypothesized that these effects were quite possibly caused by the action of OP compounds on brain ChE. However, other investigators have questioned whether the reactions described had any direct relation to ChE inhibition by OP compounds [45,46].

(c) Reproductive System Effects

Recently, several reports have appeared of chemically induced, occupationally related infertility in males. Four of five members of a farm worker crew who had intensive occupational exposure to a wide variety of pesticides complained of impotence,

according to one report [118]. The pesticides used included OP and CC compounds, triazines, carbamates, dipyridyls, and dithiccarbamates. All complained of difficulty in achieving and maintaining an erection. Normal function returned between 2 months and 1 year after cessation of exposure in all the workers. There was no neurologic deficit in any of them and no loss of libido. Oligospermia was reported in some workers poisoned by Kepone (CW Heath, Jr, written communication, January 1976).

Most recently, reports have associated 1,2-dibromo-3-chloropropane (DBCP) with infertility among workers [119]. Since the early 1950's, the fumigant DBCP has been used worldwide to control parasitic worms that attack the roots of various fruit, vegetable, and cotton plants. In July 1977, Whorton et al [119,120] investigated worker infertility in 145 employees at a major chemical company. Approximately 45% of the workers tested had sperm counts less than 40 million/ml. For this study, the authors considered normal sperm counts to be 40 million/ml or greater [120]. There also appeared to be a direct relationship between exposure duration and sperm count. Workers with sperm counts of 1 million/ml or less had been exposed for at least 3 years. No worker whose sperm count exceeded 40 million/ml had been exposed for more than 3 months. Others exposed who were not azoospermic had reduced sperm motility and increased abnormal sperm forms. Similar tests conducted by two other major chemical companies on their dibromochloropropane (DBCP)-exposed employees revealed sperm counts of less than 20 million/ml in 55% of one group and in 18% in another group [120].

One factor under consideration is the significance of duration and intensity of exposure. Although all severely affected individuals were, or had been, production workers for at least 3 years, the shortest time of exposure associated with oligospermia was only 1 year [119]. Interestingly enough, DBCP concentrations in the workplace air of affected workers were below the recommended 1 ppm airborne levels. Levels of 0.3-0.4 ppm were measured at one plant during May and July of 1977 [120]. Another important question yet to be answered completely is whether the infertility is reversible. Some return of low sperm counts toward normal after discontinuance of exposure to DBCP has been reported recently [121].

(d) Hepatic Effects

Effects on the liver have been reported for a number of pesticides including aldrin/dieldrin and endrin [122,123], 2,4-D [124], copper sulfate [125], and organotin compounds [126,127]. The reported effects range from stimulation of hepatic microsomal enzyme activity [122,123] to severe pathologic damage [126,127].

Toxicologic studies in animals have indicated that DDT and most other chlorinated hydrocarbon insecticides have caused liver damage if the dosage was sufficiently high and the exposure prolonged [2]. Actual reports of liver damage in humans have not been found, however. This may be due to the fact that early or moderate liver damage is difficult to detect in humans without histopathologic studies.

Microsomal enzyme induction by endrin has been observed. Hayes and Curley [122] performed tests on men employed in a

factory where endrin, aldrin, dieldrin, and certain OP compounds were manufactured. Workers engaged in the manufacture of endrin had increased activity of hepatic microsomal enzymes. Hunter and Robinson [123] assessed hepatic microsomal enzyme activity of workers engaged in the manufacture of pesticides by measuring changes in the urinary excretion of D-glucaric acid. Men employed in the manufacture of endrin alone had greater D-glucaric acid excretions than workers exposed to either aldrin or dieldrin. Low 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene (DDE) levels found in endrin workers also suggest enzyme induction, since DDE is metabolized by microsomal enzymes. A significant inverse relationship between the blood DDE level and urinary D-glucaric acid excretion is further evidence that these two changes are related to enzyme induction.

Bashirov [124] examined 50 individuals engaged in the manufacture of the amine salt and butyl ester of 2,4-D. Liver function was evaluated by a broad range of tests. The same analyses were conducted in 20 control subjects with no known exposure. Various liver dysfunctions were found among the exposed group including a decrease in urinary hippuric acid, changes in albumin formation, a decrease in the albumo-globulin coefficient, a decrease in the prothrombin index, a decrease in blood sugar levels, changes in the characteristic glycemic curve, and bilirubinemia. These were more pronounced in workers with longer exposures to these herbicides.

In the methyl bromide poisoning cases reported by Hine [112], some liver damage was reported. A forklift operator

responsible for transferring boxes of almonds in and out of the fumigation chambers of a nut-processing facility developed jaundice 3 months after the start of his fourth season of employment. Liver function tests were abnormal and he had clay-colored stools and dark urine. He changed jobs, and 2 years later, liver function studies were normal. Two other workers, who died, had signs of liver changes. One had moderate fatty infiltration of the liver on autopsy, and the other had an elevated serum glutamic oxaloacetic transaminase (SGOT) during his terminal illness.

Pimentel and Menezes [125] reported on three individuals who were exposed while spraying vineyards with a solution of copper sulfate neutralized with hydrated lime (Bordeaux Mixture) for prevention of mildew. Exposure varied, but in one case was as long as 12 years. All three individuals showed similar hepatic changes at autopsy or biopsy, including proliferation and diffuse swelling of Kupffer cells and formation of well-defined histiocytic or sarcoid-type granulomas containing copper.

Liver damage has been attributed to the fungicide, Brestan-60, which is composed of 60% triphenyltin acetate, 15% maneb, and 25% water. Horacek and Demcik [126] described liver damage in a Czechoslovakian spray-plane pilot who had been exposed to the fungicide Brestan-60 and other pesticides. One pilot developed indigestion and severe diarrhea after working with Brestan-60 for an unstated time. He continued to work for several days while experiencing severe heartburn and dryness of the mouth which was not relieved by drinking large amounts of

fluid. After about 1 week, his vision was affected to the extent that he could only make out the outlines of nearby objects. About 2 weeks after the onset of the initial symptoms, he had an enlarged and very tender liver and was subsequently hospitalized. Liver damage was confirmed by biopsy and microscopic examination, which showed increased collagen, moderate round cell infiltration, and slight portal and periportal fibrosis in the edges of the affected portal biliary areas; also, there was evidence of hepatocyte regeneration. Elevated serum glutamic pyruvic transaminase (SGPT) values returned to normal following dietary and insulin treatment for diabetes and vitamin and steroid therapy to improve the liver condition. Eleven months later, biopsy revealed active regeneration of the damaged liver parenchyma, and apart from a slight clinical enlargement of the liver, recovery was complete.

Another case of liver damage due to Brestan was reported [127] for a Yugoslavian formulator who had spilled a solution of the fungicide on his hands and chest while loading a plane. Redness of the skin on his chest and abdomen appeared within 3 hours and was followed the next day by the appearance of vesicles the size of wheat grains. He complained of dizziness, headache, epigastric pain, nausea, and fatigue. Upon hospitalization, his SGOT and SGPT values were elevated. Within 1 month, his SGOT value had increased to 150 units (U) and his SGPT to 575 units, respectively; and he complained of pain in the right hypochondrium, ie, over the liver. The normal ranges for these values are 8-33U/ml for SGOT and 1-36U/ml for SGPT [56]. Two

months after exposure, clinical examination revealed tenderness of the liver and enlargement to two fingers' breadth below the costal margin, resulting in a diagnosis of liver damage. At this time SGOT and SGPT values were 94 units and 196 units, respectively. Continued deterioration over the next 2 years led to a diagnosis of chronic hepatitis.

(e) Renal Effects

Effects on the kidney have also been observed in pesticide workers [128-133]. These effects range from depression of creatinine clearance and phosphate reabsorption [131] to severe tubular degeneration [128].

Davay [128] reported kidney damage in a worker exposed to methyl bromide during its manufacture. The worker was exposed during a shift when methanol and liquid bromine were being refluxed. He worked for 3 hours within a radius of about 12 feet from the sampling and filling valves near the receiving vessels. Findings revealed that methyl bromide apparently escaped from an open sampling valve which the worker noticed and closed. Three hours later he developed nausea and vomiting. Within 50 minutes, the vomiting increased in frequency and severity until the worker lost consciousness and went into convulsions. Following hospitalization, urinalysis revealed albuminuria indicating the possibility of cloudy swelling and/or tubular degeneration of the kidneys. In spite of hemodialysis and peritoneal dialysis, the worker's condition deteriorated and his renal function did not improve. Death occurred on day 18 from respiratory failure as a result of severe injury to the CNS and kidneys.

Strunge [129] reported renal damage following exposure to a mercury fungicide, methoxymethyl mercury silicate, in a 60-year-old man who had worked for 5 years as a bagger and cleaner for a firm that disinfected grain. He used no precautions and smoked and ate at his workplace. He was admitted to the hospital with edema of the genitals and lower limbs. Cholesterol, urinary protein, erythrocyte sedimentation rate, and alpha-2-globulin were elevated, and serum protein and albumin were low. Renal biopsy before treatment showed slight fibrinoid changes in the basement membrane and Bowman's capsule involving all glomeruli. He responded to steroid treatment and was discharged with diagnosis of nephrotic syndrome probably secondary to the mercury fungicide.

Morgan and Roan [130] reported a study of renal function in 65 persons occupationally exposed to pesticides. The group included 24 formulators and applicators of agricultural pesticides, 18 pest control operators, and 23 controls. The agricultural pesticides included DDT, toxaphene, parathion, phosdrin, and a variety of other OP compounds. These workers had an average of 10 years exposure. Among the pest control operators, the average experience was 7 years with exposure to lindane, chlordane, dieldrin, and other carbamate and OP compounds. Controls had no more than the ordinary household exposure to pesticides. Prior to this study, 14 of the formulators had been poisoned by pesticides, 12 requiring some hospitalization. None of these workers had been symptomatic during the 6 months preceding the test.

No differences were noted in creatinine clearance, tubular reabsorption of phosphate, amino acid nitrogen, osmolality, or free water clearance among the exposed groups. Plasma uric acid was lower in the agricultural group, and uric acid clearance was lower and resorption higher in the pest control group. No correlations were found between any of the variables and duration of employment.

Begley et al [131] cited a study of 18 workers exposed to pentachlorophenol (PCP) at a wood treatment plant. Blood and urine samples were taken from each worker on the morning of the last workday prior to a 20-day vacation, and on the mornings of the 3rd, 6th, 13th, and 20th days of the vacation. PCP concentrations in the blood averaged 5.1 ppm before vacation, falling to 2.2 ppm by the end of the vacation. Blood concentrations correlated with observed renal function measurements, which were initially abnormal but later returned to normal values. Creatinine clearance and phosphorus reabsorption values were depressed before vacation but showed significant improvement during vacation, suggesting that PCP exposure reduced glomerular filtration rate and depressed tubular function. Recovery followed a nonexposure period.

In 1966, Mann et al [132] studied kidney function in 70 spraymen and formulators occupationally exposed to various unspecified pesticides. Kidney function tests included phosphate reabsorption, urinary titratable acid, ammonium excretion after loading, and concentrating ability. Significant decreases were found in the renal function of pesticide workers compared with

those of an unexposed control group. The authors stated that chronic exposure to pesticides can result in multiple, potentially irreversible, renal tubular dysfunctions which increase with duration of exposure.

In studies with human volunteers [105] at a New York State prison, daily doses of 0.012 mg/kg carbaryl for up to 6 weeks were found to be associated with a lowering of the urinary amino acid/creatinine ratio which lessened after discontinuance of the daily doses of carbaryl for 15 weeks. This change suggested that carbaryl in this daily dose decreased kidney reabsorption of amino acids.

Tocci and associates [133] found indication of changes in kidney and liver function in persons occupationally exposed to unspecified pesticides. Changes in the functions of these organs were detected by measuring the SGOT, serum alkaline phosphatase (SAP), and creatinine concentrations. Sixteen percent of the study group showed evidence of damage to renal tubules.

(f) Dermatologic Effects

In 1975, 436 cases of skin injury due to exposure to pesticides were reported [29] in California. The pesticides implicated included: malathion, diazinon, omite, paraquat, chlordane, and difolatan. Dermatitis was a major cause of occupationally related visits to physicians. Exposure to pesticides resulted in primary irritation [53,134-138] or sensitization [139-141]. Primary irritants caused dermatitis by direct action on the skin.

A particularly severe skin problem associated with

pesticide exposure is chloracne, which is characterized by acne-like eruptions [134]. Following exposure, a delay of 6-8 weeks typically occurs before the disease is manifested, and once established, recovery may take years. This skin disease among employees of pesticide producers was first observed during the 1950's in workers at a German herbicide manufacturing plant and was caused by TCDD, a contaminant of some chlorophenol pesticides.

Twenty-nine subjects in a 2,4-D and 2,4,5-T manufacturing plant in Newark, New Jersey, developed chloracne [135]. In addition to chloracne, many of the workers also showed hyperpigmentation and increased skin fragility suggestive of the superficial lesions of porphyria cutanea tarda symptomatica. Poland et al [136] reexamined all of the employees of the same factory several years later after the level of TCDD in the 2, 4,5-trichlorophenol had been reduced from 10-25 mg/kg to less than 1 mg/kg. They found chloracne in 13 of 73 workers.

The International Agency for Research on Cancer (IARC) reported a 1949 accident which affected 288 people at the 2,4,5-T producing plant of the Monsanto Chemical Company in Nitro, West Virginia [54]. Signs and symptoms included chloracne, melanosis, muscular aches and pain, fatigue, nervousness, and intolerance to cold.

In 1976, an explosion in a chemical factory in Seveso, Italy, resulted in the release of a vapor cloud of 2,4,5-T and TCDD [137]. As a result of this explosion, an area inhabited by some 2,000 people was contaminated. The presence of TCDD was not

immediately known, so evacuation of the affected area did not begin for over 2 weeks. The first signs of skin problems were seen in local children several days after the explosion. Animal deaths were also reported. As time progressed, more than 500 people were treated for poisoning. An unspecified number of these individuals developed chloracne as a result of the TCDD exposure.

In addition to TCDD-contaminated pesticides, several other kinds of pesticides and their intermediates have been associated with chloracne. Taylor et al [138] reported 41 workers who developed chloracne as a result of exposure to 3,4,3',4'-tetrachloroazoxybenzene (TCAB) during the manufacture of the herbicide 2-(3,4-dichlorophenyl)-4-methyl-1,2,4-oxadiazolidine-3,5-dione. In most of the workers, the chloracne appeared during their first 2 months of employment, but varied overall from 1 week to 8 months. Family members of four workers also developed chloracne, probably due to contaminated work clothes or tools being carried home.

Deeken [134] reported six cases of chloracne from occupational exposure to 2,6-dichlorobenzonitrile (dichlobenil). Those involved were exposed either during dumping of dichlobenil powder into a slurry during formulation or during bagging of the final product. The lag-time between initial exposure to the compound and the development of the acneiform eruptions varied, ranging up to 5 months. The eruption generally consisted of several hundred open pinpoint comedones. No acne cysts were observed. As long as exposure continued, response to the usual

forms of treatment was poor. Once contact with dichlobenil was stopped, improvement occurred.

A variety of other skin reactions have been reported in response to pesticides [142-145]. Kazen et al [142] studied a termite control operator who had habitually used his left hand to protect his face while he sprayed chlordane and aldrin with his right hand. The man subsequently developed a severe dermatitis of the left hand.

Brown [143] reported "skin flushes" or sudden reddening, usually of face and forearm, in 17 employees of a triazapentadiene manufacturing plant. The flushes were reported to last from an hour to a couple of days and usually occurred after the consumption of alcohol.

Radimer and colleagues [144] presented four cases of epidermal necrolysis in individuals whose homes were fumigated with a mixture containing acrylonitrile and carbon tetrachloride. The first evidence of skin disease appeared 11-21 days after their initial exposure to the fumigant. The skin condition was characterized by patches of intense tender erythema that rapidly progressed to huge blisters that opened. Three of the four patients were adults and they died from shock and/or gastrcintestinal bleeding.

Bisby and Simpson [145] reported a case of dichlorvos poisoning manifested by an acute skin reaction in a male pest control operator who had worked with pesticides for more than 9 years. One month earlier, he noticed a slight burning sensation of the skin after contact with dichlorvos. The skin was washed

with no further ill effect. The poisoning episode occurred during the routine spraying of a 1% solution of dichlorvos. Some of the chemical leaked onto the operator's shoulder and slight local irritation occurred. The operator stopped, put on clean overalls, placed a plastic sheet between the spray unit and his back, and completed his work, all without washing. During the day he noticed increasing local irritation and burning of the contaminated area, and at the end of his shift, excessive tiredness. Three days later he had extensive areas of erythema and bullae typical of acute contact dermatitis. ChE activity levels were extremely low indicating severe systemic OP poisoning. There were no other signs of clinical abnormalities. Exposure to pesticides was avoided, recovery was uneventful, and the patient returned to work after a month of rest.

Several pesticides have caused skin hypersensitization, an allergic reaction, in humans [139-141]. Patch tests are often done to determine whether a suspected compound is the sensitizer.

Edmundson and Davies [139] reported occupational dermatitis in four workers exposed to naled while cutting chrysanthemum plants. The women involved had been doing this type of work for from 1 month to 9 years. On the day of the incident, the field in which they were working had been sprayed with a mixture of naled, captan, and dicofol, and some of the plants were still wet with the solution at the time of cutting. While in the field, all four women experienced burning and itching of the face, neck, and arms, and later, welts and/or rashes. Contact sensitization type dermatitis was the diagnosis.

Patch tests carried out 2 weeks later showed a positive reaction only for naled in each woman.

Spencer [140] reported three farmers who developed acute dermatitis after spilling the herbicide allidochlor, a derivative of 2-chloroacetamide, on their shoes or clothing. All three developed a violaceous eruption with bullae on contact areas. Patch testing a few months later on two of the individuals resulted in a 4+ (strong) response for allidochlor, and was negative for other pesticides that they had used.

Milby and Epstein [141] described the experimental testing of the sensitivity of volunteers to malathion. Eighty-seven men were divided into four groups. The malathion used was 95% pure, analytical standard grade malathion in ethanol. In Group I the skin was first irritated by a 3-second freeze with dichlorodifluoromethane to enhance sensitization, and then 10% malathion was applied. In Group 2, 10% malathion was applied to a nonirritated skin site. Groups 3 and 4 were first irritated with dichlorodifluoromethane and then exposed to 1.0 and 0.1% malathion, respectively. In 30 days, all subjects were retested with a nonirritating 1% concentration of malathion in ethanol at a new site. The findings indicated that a single exposure to 10% malathion readily induced contact sensitization in almost half of the subjects, and the average intensity of the reactions was great. Weaker solutions had much less tendency to sensitize, even when applied to irritated skin. To explore the degree of sensitivity, a group of five highly malathion-sensitive subjects were tested with weak solutions of malathion in water and

acetone. All gave strong reactions (bullae) at a 1 ppm concentration in acetone, and positive responses were also evoked by applying a commercial preparation of 0.9% malathion in water.

A subsequent study of two groups who used malathion in their occupations (157 mosquito abatement workers and 43 poultry workers) revealed that about 3% reacted to a 1% malathion patch test. Several of these individuals gave histories of previous episodes of dermatitis which had defied diagnosis.

The herbicide monuron has also been associated with contact dermatitis [146]. Two episodes are included in EPA's Pesticide Episode Review System data.

(g) Ophthalmologic Effects

In 1975, 314 eye injuries were reported in California due to pesticide exposure [74]. Most eye injuries were acute, characterized by damage to the conjunctivae, cornea, and associated structures because of the corrosive properties of pesticide active ingredients or formulations [29,143]. A variety of pesticides have been associated with such injuries, including triazapentadienes, weed oil, and difolatan.

Brown [143] reported three workers in a plant manufacturing triazapentadienes who experienced intense eye irritation 6-12 hours following their workshift. Two of the three were admitted to a hospital. One had a large area of corneal de-epithelialization, and the other had superficial punctate keratitis. The injuries were traced to escaping vapors of ethanol, isopropyl alcohol, and formidines from a leaking valve in the recycling part of the plant.

Maddy and Topper [29] described eight cases of eye injury in persons working in pesticide manufacturing and formulating plants. In one case, an employee was exposed to weed oil when the nozzle he was using to fill a can broke off and sprayed his face, chest, and legs. He was treated for chemical burns to the eyes. Another case involved an employee working with a dust collector. Some difolatan powder blew through the side vents of his goggles and caused chemical irritation in his left eye. A third case of eye injury involved an employee emptying a drum of lime sulfur. While he was setting the drum down, the top opened and some liquid contacted his face and eyes. Although he was wearing safety glasses, his eyes were nevertheless injured.

Cataracts are often considered to be a condition of old age. However, pesticides have been implicated in the production of lens and corneal cataracts. The pesticide compounds 2, 4-dinitrophenol (DNP), used both as an herbicide and as a fungicide, and dinitro-o-cresol, used as an insecticide, were implicated in the 1930's as causing cataracts after large doses were ingested for weight control purposes [51].

(h) Respiratory System Effects

Inhalation is an important route of exposure for pesticides. After inhalation, pesticides gain access to the bloodstream, and systemic toxicity can result. In some cases, inhalation of pesticides can also result in local damage to the respiratory system itself, ranging from localized burning in the mouth and throat [147] to pulmonary fibrosis [125,148].

Pimentel and Menezes [125] reported three cases of

vineyard sprayer's lung. The three men were all exposed while spraying vineyards with a solution of copper sulfate neutralized with hydrated lime (Bordeaux Mixture) for the prevention of mildew. Case 1 was exposed on the job for 3 years, Case 2 for 12 years, and Case 3 for an unspecified length of time. Case 1 had symptoms for 3 years prior to hospitalization. He was dyspneic and cyanotic when hospitalized. A chest X-ray showed diffuse bilateral reticular and micronodular shadows. Pulmonary function studies showed a restrictive ventilatory defect. The patient died of bilateral spontaneous pneumothorax. Autopsy showed bilateral diffuse pulmonary fibrosis with emphysema in lower lobes. Histology indicated numerous histiocytic granulomas and fibro-hyaline nodular scars. These lesions contained abundant inclusions of copper. Case 2, an alcoholic, was hospitalized for a febrile syndrome. A chest X-ray showed reticular and micronodular shadows. The liver was irregular and hard. The patient's condition deteriorated progressively until he died. Autopsy showed numerous blue nodules and extensive fibrosis in both lungs. Histologically, there were numerous histiocytic granulomas and extensive nodular scars. The lesions contained considerable amounts of copper. Case 3 was hospitalized for weakness, joint and muscular pains, and loss of appetite. A chest X-ray indicated increased lung markings and possible pneumonia with pleural reaction. The liver was enlarged. Biopsies of both the liver and lung were made. Histology showed histiocytic granulomas that were in an advanced condition of sclerosis and hyalinization in some areas. These lesions

contained abundant inclusions of copper.

Warraki [147] reported two cases of acute bronchopneumonia in agricultural workers exposed to toxaphene sprays. The first man reported he had been heavily exposed to toxaphene for 2 months. A chest X-ray revealed marked bilateral hilar lymphadenopathy with fine miliary opacities heavily distributed over both lungs. Pulmonary function tests demonstrated a vital capacity 36.2% and a maximum breathing capacity 19% of predicted normal. The second man had been heavily exposed to toxaphene spray for the first time 1 month before entering the hospital. A chest X-ray showed coarse miliary shadows in both lungs with maximum distribution in the middle zone. Pulmonary function studies demonstrated a vital capacity of 22% of predicted normal. Both men showed dramatic improvement with avoidance of exposure and treatment with corticosteroids.

Weiner [148] reported a case of bronchial asthma attributed to exposure to an OP pesticide in a 41-year-old chemical formulation worker with a history of rhinitis and 21 years' exposure to sulfur powder, who had recently begun packaging mevinphos. When a leak developed in a can he was using as a filler, he removed his mask and gloves to fix the leak. During this time he inhaled a large quantity of the material and spilled some on his hands. Thirty minutes later he was hospitalized with labored breathing, cyanosis, and miosis. Moist rales were present throughout the lungs. The man responded to atropine treatment. Three weeks later while working with unspecified powders, he had coughing, wheezing, and labored breathing. Over

the next 3 years he had repeated bouts of pneumonia, and pulmonary function studies showed decreased forced vital capacity on two occasions. The authors speculated that the observed susceptibility to respiratory effects occurs only in subjects predisposed to allergy.

Paraquat has caused pulmonary edema, severe irritation of mucous membranes, and acute renal failure, usually after accidental or suicidal ingestion. If the immediate effects do not produce death within a week, the patient may either recover fully or die in the delayed stage of the poisoning. This is characterized by rapid development of pulmonary fibrosis, with the appearance of granular opacities on radiographs of the chest. The patients become dyspneic from the combined effects of decreased pulmonary capacity of the lungs. Death from respiratory failure and anoxemia occurs 2-4 weeks after the poisoning [149].

Such progression of pulmonary fibrosis was observed by Davidson and Macpherson [150] in two cases of paraquat poisoning due to accidental ingestion of Gramoxone W. In the first case, pulmonary function was normal until day 7 following exposure. On day 7 a chest radiograph showed fine granular opacities. Thereafter, lung function tests showed rapid deterioration. Open biopsy on day 9 showed interstitial edema, fibroblastic activity, and fibrosis. Following death on day 17, an autopsy showed the lungs to be enlarged and almost solid throughout. Interstitial tissue showed considerable fibrous thickening, disorganizing the lung structure. In places, air spaces were lined by a thick

membrane resembling hyaline membrane disease. Reactive hyperplasia was seen in many areas. In the second individual, ill-defined opacities were evident on day 6 following exposure. The patient experienced respiratory distress and lung function showed rapid deterioration. After death on day 25, autopsy showed complete obliteration of the air spaces by fibroblastic proliferation and inflammatory cells. The alveolar walls and interstitial tissue were broadened by fibrous tissue. Both upper lobes showed gross emphysema.

Barthel [151] cited data on three of five cases of lung fibrosis found in pest control workers. The workers had many years of experience during which they were exposed to several pesticides including OP compounds, OC's, and arsenates. X-ray examination of the lungs revealed disseminated foci mainly localized in the lung periphery and diffuse spotted and striped lung shadows with signs of diffuse emphysema.

(i) Hematopoietic Effects

Pesticide exposure has been associated with hematologic alterations [152-159]. Toxic materials may affect the components of the blood by influencing their production, rate of peripheral destruction, or distribution [55].

Furie and Trubowitz [152] reported a case of chlordane exposure followed by the development of megaloblastic anemia. The individual mixed a chlordane solution and then poured it around the inside and outside of his house/office for termite control; during this operation, chlordane was spilled on his hands. Actual total skin contact was estimated to be about 3-5

hours during a 2-month period. Chlordane fumes were very strong in his office where he spent approximately 300 hours during a pericd of 6 months. After that time, he experienced severe shortness of breath, fatigue, and tachycardia. Hematologic analyses revealed anemia with the presence of megaloblasts. Examination of the bone marrow confirmed hypercellularity. A diagnosis of megaloblastic anemia was made. As the patient's hemoglobin levels increased after a series of blood transfusions, his condition gradually improved.

Sanchez-Medal and coworkers [153] noted 20 cases of aplastic anemia during 8 years at Hospital de Enfermedades de la Nutricion in Mexico City. In 16 of the 20 cases, pesticides appeared to be the only possible offending agents since all patients had repeated contact during the 6 months preceding clinical onset of their disease. The insecticides involved were DDT alone, or DDT in association with lindane, dieldrin, or DDVP. Clinical and laboratory findings in these cases did not differ from those in aplastic anemia due to other causes. Also reported was the case of a 13-year-old boy hospitalized with aplastic anemia which was circumstantially related to DDT. The boy's home had been repeatedly sprayed with DDT for 2 years, and in the 4 months preceding his hospital admission DDT was sprayed every other day. The patient was recovering when he was accidentally reexposed in his hospital room when a volunteer sprayed a 10% DDT spray. He had an anaphylactic reaction within 1 hour of reexposure, and his blood dyscrasia worsened. He died 30 hours later.

The American Medical Association registry on blood dyscrasias reported 44 cases of aplastic anemia associated with pesticides through 1963 [154]. Of these cases, 13 were related to lindane, and in 7 cases, lindane was the sole agent; 19 cases were related to DDT, and in 3, DDT was the sole agent; 12 cases were related to chlordane, and of these, chlordane was the sole agent in 4 instances.

Palva et al [155] reported the case of a 64-year-old farmer who was spraying 2-methyl-4-chlorophenoxyacetic acid (MCPA) with a manual sprayer that leaked, so that his clothing became soaked with the herbicide. Two weeks later he had spontaneous hematomas and manifested lethargy. He was pancytopenic 2 months later. He resporded to steroid treatment within 2 months and was free from symptoms in 5 months.

Samuels and Milby [156] conducted a further study on a lindane exposed population first studied by Milby et al [157]. The population included 79 individuals who had been exposed daily to lindane for a period of weeks to years. Seventy-one of these 79 were employed in lindane processing plants. The other 8 individuals included the residents of two households in which lindane vaporizing devices were operated for pest control purposes. Milby et al [157] found that the concentration of lindane in the blood reflected recent lindane absorption. The mean concentration of lindane in the blood appeared to be a valid indicator of relative exposure intensities; however, levels did not appear to increase with increasing duration of exposure. Samuels and Milby [156] found isolated instances of leukopenia,

leukocytosis, granulocytopenia, eosinophilia, monocytosis, and thrombocytopenia in the same population. Pancytopenia with reticulocytopenia was not observed. There did not appear to be a correlation between abnormal findings and either duration or intensity of exposure. Monocytosis appeared to decline after the 5th year of employment in 57.7% of the cases.

West [158] reported the case of a girl with an atypical blood count and anemia. In addition, four other members of her family had mild anemia. All recovered when a lindane vaporizer which had been operating for 1.5 years was removed from the home.

Davignon et al [159] reported a 3-year study of three groups: 441 apple-growers who had worked with insecticides, 170 subjects who did not actually use insecticides but lived in or near orchards, and 162 controls with no known contact with insecticides. No difference was observed in average RBC counts and hemoglobin concentration in the three groups. However, the average leukocyte count was significantly lower for the apple-growers and those living near orchards than for controls, although levels in both groups were within the range of the normal population.

(j) Cardiovascular Effects

Few reports are available on the effect of pesticides on the cardiovascular system. Health surveys of workers with intense occupational exposure to DDT have not detected cardicvascular changes [160].

Butzingeiger [161] examined 180 vinedressers and cellarmen who had used arsenic insecticides and who had expressed symptoms

consistent with chronic arsenic intoxication. Of the 180 examined, 41 (22.8%) showed evidence of vascular disorders in the extremities. Of the 15 cases described in detail, cold hands or feet, or both, were common and apparently preceded the development of gangrene on the toes or fingers in six cases.

Electrocardiogram (ECG) findings of vinegrowers with chronic arsenic intoxication were reported by Butzengeiger [162]. Of 192 ECG's, 107 (55.7%) were normal, 30 (15.6%) showed slight changes which alone were insufficient for definite diagnosis of cardiac damage, and 55 (28.7%) revealed definite changes. In 19 of the 55 altered ECG's, changes were attributed to age, arteriosclerosis, or intercurrent disease. In the remaining 36, arsenic poisoning was considered responsible. ECG abnormalities included Q-T prolongation and flattened T-wave. Follow-up studies revealed a decline in ECG abnormalities along with the symptoms suggestive of diminution of arsenic intoxication.

Overexposure to OP insecticides has been associated with blood coagulation and vascular changes [163]. In one male over 50 years of age, two cerebrovascular incidents followed overexposure to disulfoton (GE Quinby, MD, written communication, May 1978).

Blood pressure elevation has been sporadically reported [164-166] but no well-controlled study has been done of the relationship to pesticide exposure. Sandifer et al [164] reported on a long-term study of pesticide-exposed workers in which systolic blood pressure was elevated among a cohort of formulators and pest control operators as compared with matched

controls. This elevation was correlated with blood DDT and DDE levels. There were no differences between exposed and controls in smoking, family history of hypertension or diabetes, and educational level.

Richardson et al [165] studied 23 pesticide formulatcrs exposed to various pesticides including chlorinated hydrocarbons, eg, DDT, OP compounds, eg, parathion, and carbamates, eg, carbaryl. The 23 exposed formulators and 20 controls were tested for catecholamine and cortisol metabolism. Blood pressure was measured in all. Epinephrine and norepinephrine concentrations in plasma and urine were lower in the exposed group, while urinary metanephrine concentrations were similar in both groups. Mean systolic blood pressure was higher in the exposed group and correlated significantly with blood DDT levels.

Morton and coworkers [166] examined the effect of pesticide exposure on blood pressure. The blood pressures of 153 pesticide workers from 28 different pesticide manufacturing and formulating plants in Oregon and of 76 controls were measured. Sixty-nine of the workers were from one phenoxy herbicide plant. The controls were medical center employees. No difference was found in mean systolic and diastolic blood pressure among the three groups, but 38% of the phenoxy herbicide workers had systolic blood pressure greater than 150 and/or diastolic blood pressure greater than 90, compared with 29% of all other pesticide workers and 30% of controls. There was a higher frequency of family history of hypertension in the herbicide group, suggesting that the workplace had little influence on the frequency of hypertension

in the workers studied.

(k) Carcinogenic Effects

Relating specific causative agents to cancer in humans is a difficult task and requires properly designed epidemiologic studies. These studies involve the correlation of an increase in cancer incidences as compared with expected incidence among occupationally exposed workers. Such correlations are difficult because workers typically have repeated exposures to multiple substances in the workplace. Furthermore, workers are often transient, which makes these studies much more difficult.

Arsenical pesticides have been shown to cause human cancer. Roth [76] described 47 German vinegrowers chronically poisoned by occupational exposure to arsenical insecticides in the vineyards and by arsenic-contaminated wine. Cancer was listed as the cause of death in 30 of the 47 cases (64%), and malignancies were observed in an additional three cases. In the 33 subjects with malignancies, a total of 75 tumors was found including tumors of the lung, skin, liver, larynx, bile duct, esophagus, and tongue. Bronchial cancer was listed as the cause of death in 16 cases, and 6 of these individuals also had from 1 to 4 skin cancers. In the 2 cases where death was attributed to cancer of both lungs, both subjects also had skin cancer and 1 had cancer of the larynx. The individual who died of cancer of the bile duct also had a bronchial carcinoma. Of the 6 individuals with liver sarcomas, 1 also had 2 skin cancers. And, of the 5 cases with esophageal cancer, 1 also had cancer of the tongue and another had 3 skin cancers. In the 3 individuals who did not die from

their malignancies, 18 skin cancers were found. In 8 cases, "arsenic cirrhosis" was listed as a cause of death and was observed in an additional 25 cases.

In another study, Baetjer and coworkers [50] discussed the mortality of retired workers with exposure to arsenical pesticides during the manufacture of calcium, sodium, and lead arsenate. Of 22 deaths among the retirees, 17 were due to cancer. The expected cancer deaths for the group was 4.43, based on the general Baltimore population. By site, the ratio of observed to expected cancer deaths was 10/1.49 (6.71) for respiratory cancer, 3/1 (3.0) for lymphatic and hematologic cancers (lymphosarcomas), and 4/2.69 (1.49) for all other neoplasms. A death rate analysis was also conducted, and once again, cancer mortality was found to be significantly increased.

In a study by Axelson and Sundell [59], an excess of all cancer types was found in Swedish railway workers who primarily used amitrole (a triazole derivative), 2,4-D, and 2,4,5-T. The elevated incidence of cancer seemed primarily associated with exposure to amitrole and combinations of amitrole with other pesticides. This compound has also been shown to be carcinogenic in animals [58].

NIOSH has recommended that acrylonitrile be handled in the workplace as a probable occupational carcinogen [69]. This recommendation is based on the results of animal studies and a recent preliminary epidemiologic study of 470 textile workers exposed to acrylonitrile during polymerization which indicated an excess incidence of lung and colon cancer among workers with

potential acrylonitrile exposure. A total of 16 cancer cases occurred between 1969 and 1975 among the cohort first exposed between 1950 and 1955; only 5.8 cancer cases would have been expected, based on company rates (excluding the cohort). However, as is commonly the case, workers may have been exposed to a variety of other chemicals which may have acted on the biologic system synergistically. Also, the results of the study are preliminary, approximately one-third of the cohort having been studied [81].

The NIOSH criteria document on coal tar products [82] included an evaluation of the biologic and health effects of creosote. Overexposure to creosote caused burns, conjunctivitis, depression, headaches, vertigo, transitory confusion, and nausea [82]. Squamous-cell carcinomas were also reported for a creosote factory worker and a painter who scoured with creosote [82]. Skin tumors were found in cresote-treated mice, rats, and dogs, and lung tumors were found in mice. NIOSH has recommended that creosote be handled in the workplace as a probable carcinogen [82].

Benzene has been associated with a variety of hematologic abnormalities including leukemia. Forni and Vigliani [77] estimated that at least 150 benzene-related leukemia cases have been reported. In addition to these case reports, several epidemiologic studies have also associated benzene with cancer. McMichael [78] studied a cohort of rubber workers with solvent exposure. The results suggested an increased risk of death from lymphatic leukemia in those exposed to solvents. The authors

demonstrated a dose-response of both duration and intensity of solvent exposure with lymphatic leukemia.

Infante et al [79,80] reported results of an epidemiologic study of Pliofilm workers exposed to benzene. The study identified a statistically significant excess incidence of leukemia in benzene exposed workers compared to a nonexposed control population. A fivefold excess of total leukemia and tenfold excess of myelomonocytic leukemia were found. NIOSH has recommended that benzene be handled in the workplace as a probable carcinogen and OSHA has also regulated the compound as an occupational carcinogen.

Certain compounds of hexavalent chromium have also been implicated as carcinogens on the basis of human and animal studies. Chromium compounds implicated in these studies have lead NIOSH to infer that all hexavalent chromate salts of alkaline earth metals are probable human carcinogens and this would include the pesticides zinc mercury chromate and copper zinc chromate [83].

Barthel [167] investigated the tumor incidence in 316 long-term exposed pesticide workers in the Newbrandenburg district of Germany. There were 30 cases of tumors of which 11 were bronchial carcinomas. The incidence of bronchial carcinoma in the group was 20 times that expected in an age-specific general population. Frequency at all other cancer sites did not differ significantly from expected. Exposure to pesticides ranged from 6 to 23 years and included phenoxyacetic derivatives, OC's, OP's, organic nitro derivatives, and some arsenic

compounds. Since the workers were exposed to various chemical compounds simultaneously or alternately, the carcinogenic effect could not be associated with any one specific pesticide.

Although the literature contains numerous reports of pesticide poisonings, many of these resulted from exposure modes that are not usually experienced in the workplace. In those cases where the exposure took place during the manufacture or formulation of pesticides, exposures were seldom limited to a single substance. Evaluation of the hazard involved in the manufacture of pesticides is further complicated by the scarcity of successful epidemiologic studies. Epidemiologic studies are hampered by the difficulties involved in identifying a suitable cohort of employees and control group. In view of the limitations encountered in both poisoning cases and epidemiologic studies, it is important to use animal test results to predict and, in some cases, to reinforce effects in humans.

Effects in Experimental Animals

Toxicologic evaluations of pesticides have for many years focused on common laboratory animals as the experimental model for man's physiological, biochemical, metabolic, and pathological response to these chemicals. These evaluations have produced a large body of information on the local and systemic effects of pesticides in animals. In recent years there has been an emphasis on obtaining better information on chronic exposure effects. This emphasis has led to the finding that some pesticides are animal carcinogens. In addition, other

irreversible effects such as teratogenicity, mutagenicity, and reproductive disorders have been observed in animals. In the following sections, various aspects of acute and chronic pesticide toxicity will be discussed.

(a) The Acute Toxicity of Pesticides

While acute toxicity determinations have been conducted in various animal species including the rat, mouse, hamster, guinea pig, rabbit, cat, dog, and monkey, such measurements are most commonly made in the rat and the mouse. The large body of toxicity data which exists for these two species makes it possible to evaluate the toxicity of a pesticide relative to other pesticides.

A number of genetic and environmental factors contribute to the variability of acute toxicity. One major factor is the difference in the susceptibility of the exposed individuals of any species, including man. While individual variability among animals and man is not predictable, other variables are. Animals of the same strain but of different sexes often provide marked differences in the acute LD50's when tested. Comparisons of the oral toxicity of 85 pesticides by Gaines revealed male-female sex ratios of the LD50's ranging from 0.21 to 4.62 [99]. Variability also occurs between different routes of exposure. Gaines determined that the ratio of dermal-oral LD50's for 57 compounds tested by both routes ranged from 0.2 to 21.0.

Old and young animals of one species may differ rather markedly in their response to pesticides as shown by differences in their acute LD50's. Brodeur and DuBois [168] tested 16 OP and

carbamate compounds in both adult and weanling rats and found that 15 were more toxic in weanling than in adult rats by LD50 ratios that varied from 1.25 to 4. Only schradan was more toxic to adults and by a ratio of 5 to 1. Increased susceptibility of newborn animals to toxic agents can be explained as resulting from the undeveloped state of the detoxication mechanisms of newborn animals [168]. Lu et al [169] found that DDT and dieldrin were 20 and 5 times as toxic, respectively, to adult as to newborn Wistar rats, whereas, 99.6% malathion was almost 30 times as toxic to newborn as to adult rats [169].

An effect of ambient temperature on toxicity has also been demonstrated. Increased toxicity with increased temperature has been found by Furman et al [170] for DNP.

Diet also modifies acute toxicity. The presence of fat in the diet has a tendency to increase the absorption of nonpolar pesticides and thus lower acute LD50 values. Both rats and mice demonstrated increased toxic effects from DDT on a 15% fat diet compared to a 5% fat diet. The protein content of diets can also modify the degree of acute toxicity [171]. Boyd and Krijnen [171] showed a marked increase in carbaryl toxicity in rats on a protein deficient diet. The oral LD50 of carbaryl was reduced from 575 mg/kg on a 27% protein diet to 84 mg/kg on a 3% protein diet.

The toxicity of a pesticide can be increased or decreased if it is present in animal or man in conjunction with another active compound which affects its metabolism. Potentiation is often the result of inhibition of detoxification mechanisms,

whereas antagonism is often the result of enzymatic detoxification [172-174]. Experiments have shown that certain pesticides dramatically potentiate the toxicity of other pesticides. Frawley et al [175] observed that the lethal doses for EPN and malathion when administered separately to dogs were 200 mg/kg and >4,000 mg/kg, respectively. However, when they administered the pesticides simultaneously, the dogs died at dose levels of 2 mg/kg EPN and 100 mg/kg malathion. This synergism extended to the inhibition of erythrocyte ChE. Subchronic feeding of both compounds to dogs produced low blood ChE inhibition at exposure levels one-half to one-thirtieth of those required for the separate compounds to exert similar effects. Similar experiments conducted with rats resulted in increased ChE inhibition but to a lesser extent than in dogs [175]. Other mechanisms for potentiation and antagonism also exist [172,173].

The presence of OC pesticides, such as dieldrin, has reduced the toxicity of several OP pesticides. Apparently the OC stimulates enzymatic detoxification of the OP [172,173].

Another factor affecting toxicity is fractionation. This concerns the time over which the total dose is administered or the administration of the total dose in smaller subunits. Normally, fractionated administration allows more time for the pesticide to be detoxified or excreted. Where the toxic agent is actually the metabolite of the pesticide, such decreased toxicity may not result [176].

Obviously, toxicologic mechanisms of pesticides are far more complicated than acute testing normally reveals.

Variability in toxicity according to sex, age, route of exposure, diet, environment, and multiple exposures certainly applies to humans as well as to experimental animals. Factors affecting toxicity of pesticides in the workplace should always be considered, especially in light of the range of susceptibility exhibited by most heterogeneous populations.

While the previous discussion of acute toxicity applies to a general understanding of the subject, some studies have elements deserving special consideration. Inhalation and dermal toxicity studies deserve elaboration in view of their relation to occupational exposures.

(1) Inhalation Toxicity Studies

Study of the toxicities of substances in animals by inhalation is of great significance to the field of industrial toxicology. Except for iv injection, inhalation is the most effective and rapid route for the entry of substances into the body and for production of toxic effects. Many of the problems of worker-induced systemic toxicity have resulted from inhalation exposure as described earlier.

Because chronic inhalation toxicology experiments are expensive and difficult to perform, relatively few long-term studies of this nature have been performed for pesticides, despite their importance. Such experiments require that animals be placed in special exposure chambers that have intake and exhaust systems as well as some mechanism for maintaining a consistent and measurable concentration of the pesticide. These experiments are difficult to conduct, especially for studies of

dusts. In many experiments, animals are often removed from the inhalation chamber and replaced on an established regimen during the experimental period.

Because of the experimental difficulties, a single discrete dose cannot be administered, and few experiments utilize the same period of exposure, making dose comparison difficult. The observed toxicity value may be different from that obtained orally because chemicals absorbed through the lungs partly bypass the liver, where most detoxification occurs. On the other hand, some compounds are actually activated by liver enzymes, eg, parathion, and in this case, the direct path to the liver resulting from oral administration could result in greater toxicity than would be expected through inhalation.

(2) Dermal Toxicity Studies

The term dermal toxicity includes the production of local effects on the skin and of systemic toxic effects by cutaneous absorption of pesticides.

Because of the importance of contamination of the skin in the industrial setting, many acute dermal toxicity experiments of pesticides have been conducted. Dermal exposure may be a particularly hazardous aspect of occupational contact with pesticides because workers may not be aware that certain compounds have a remarkable ability to penetrate the skin. Gaines [177] has found a closer relation between the dermal toxicities of some pesticides in rats and the occurrence of occupational poisoning than between oral toxicities and occupational poisoning. He reported that dieldrin has an oral

LD50 in the same order of magnitude as lindane and DDT, 46, 88, and 113 mg/kg, respectively. However, at that time Hayes [178] had reported 100 cases of dieldrin-related occupational poisoning. Gaines was not aware of any occupational poisonings associated with DDT or lindane, but he speculated that this phenomenon was due to dieldrin's dermal LD50 of 90 mg/kg as compared with those of lindane (1,000 mg/kg) and DDT (2,510 mg/kg) [177].

Local skin effects produced by pesticides are also of major concern and include local irritation and the development of hypersensitivity (allergic reactions) to the substances. The irritancy or direct dermal toxicity of compounds is commonly evaluated by applying the compound to the shaved skin of the rabbit. Allergenicity or hypersensitivity frequently is evaluated by applications to the shaved skin of guinea pigs.

(b) Chronic Toxicity

Studies of chronic toxicity in animals have not been reported in the open literature for the majority of registered pesticides. Studies that have been reported have resulted in the observation of irreversible toxic effects which have not been detected by acute toxicity studies. The organ most frequently damaged is the liver, the major site of detoxication of chemical substances. The CNS, the peripheral nerves, the kidneys, and other organs may also be irreversibly affected. The major irreversible effects observed in experimental animals and in in vitro test systems include carcinogenesis, mutagenesis, teratogenesis and other reproductive effects, and neurotoxicity.

While testing for mutagenesis and teratogenesis does not necessarily involve chronic exposure, such effects are severe enough to warrant discussion here. Mutagenesis testing itself may require a multigenerational study to detect affected individuals. All of these will be discussed in the following sections. From an occupational point of view, dermal and inhalational exposures in chronic animal studies are more applicable to the actual workplace situation than is oral exposure.

(1) Carcinogenesis

Much concern for the health of workers in the pesticide industry centers around the possibility that they may be developing cancer as a result of their exposure to compounds in the workplace. As discussed earlier, exposure to arsenical pesticides has been associated with increased risk of developing skin cancer, leukemia, and lung cancer in pesticide workers [48]. Exposure to vinyl chloride, a pesticide intermediate, has resulted in the induction of liver cancer [179]. The finding of similar tumors in experimental animals [180] and in workers exposed to vinyl chloride has lent credence to the belief that animal toxicity experiments are significant in judging whether induction of human cancer by a given chemical is likely.

Inorganic arsenic compounds, acrylonitrile, benzene, amitrole, certain hexavalent chromium compounds, and creosote, all of which have been reviewed earlier in the document, are considered by NIOSH to be probable carcinogens based on evidence from both humans and experimental animals. The following is a

review of 113 additional pesticides with respect to carcinogens based on evidence from both humans and experimental animals. Of the 113 compounds reviewed, 26 (see Table XIV-8) are considered suspected occupational carcinogens based on evidence found in animals and presented herein. Carcinogenicity data are reviewed also for 27 pesticides for which the evidence for or against carcinogenicity in test animals is inconclusive. These compounds require further testing before they can be termed suspected occupational carcinogens or placed in the final group of pesticides for which data from experiments with animals have their carcinogenic potential. Of the 113 compounds reviewed, 26 (see Table XIV-8) are NIOSH has placed 60 pesticides in this final category. Remaining unreviewed are approximately 1,300 pesticides for which data were not available.

(A) Suspected Occupational Carcinogens

NIOSH recommends that the following pesticides should be handled in the workplace as suspected occupational carcinogens. Pesticides are included in this classification if laboratory studies indicate a statistically significant relationship between tumor development and pesticide administration in one or more mammalian species.

(i) Aldrin/Dieldrin

After reviewing the available world literature, NIOSH has determined that aldrin and dieldrin should be handled in the workplace as suspected occupational carcinogens [2]. The International Agency for Research on Cancer (IARC) reviewed the literature on the carcinogenicity of these two

compounds in 1974 and found no evidence for the induction of cancer in animals by aldrin, but did link aldrin with its metabolite dieldrin. Dieldrin was concluded to be a hepatccarcinogen in mice [181]. In 1972, EPA concluded that dieldrin was a carcinogen in the mouse [182] and restricted its usage based partially on that conclusion (Federal Register 39:7246, October 18, 1974).

(ii) Bis(2-chloroethyl) Ether

Bis(2-cholorethyl) ether was administered by Bionetics Research Labs [4] daily by stomach tube to two groups of 18 male and 18 female B6C3F1 and B6AKF1 mice at a rate of 100 mg/kg for 21 days. This was part of a screening study in which 106 pesticides were tested for carcinogenicity for NCI. The chemical was subsequently administered at a concentration of 300 ppm in the diet for 80 weeks. Hepatoma incidence was 14 tumors/16 male B6C3F1 treated mice and 9 tumors/17 male B6AKF1 treated mice compared with 8 tumors/79 and 5 tumors/90 male control mice of the respective strains. The incidence in females was 4 hepatomas/18 and 0/18 treated mice compared with 0 tumors/87 and 1 tumor/82 in the controls of the respective strains. Hepatoma incidence was significant at a level of P=0.01 [4].

In the same study [4], subcutaneous injections of 215 mg/kg were administered once per animal to the same strains. Reticulum cell sarcomas occurred more frequently in the treated mice than in controls (P=0.01). In B6C3F1 males, the incidence of sarcomas was 4/15, while B6AKF1 males had an incidence of 2/14

compared with 8/27 and 0/8 in controls, respectively. Females had 1/17 and 1/18 in treated animals and 1/9 and 5/17 in controls, respectively [4]. The IARC reviewed the literature in 1975 and found bis(2-chloroethyl) ether to be an animal carcinogen [183].

(iii) Bis(2-hydroxyethyl)dithiocarbamic Acid, Potassium Salt

In the Bionetics study reported in 1968 [4], 18 male and 18 female B6C3F1 and B6AKF1 mice were administered 464 mg/kg bis(2-hydroxyethyl)dithiocarbamic acid, potassium salt, by oral intubation at 7 days of age. The same amount was given daily until the mice were 28 days old, at which time the compound was mixed with the ground feed at 1,112 ppm; the diet continued for 80 weeks. The total number of mice that developed tumors was significant at a level of $P=0.01$; the occurrence of hepatomas among the tumor types was also significant at the same level. In male B6C3F1 treated mice, 16 tumors developed in 14/16 (88%) mice; 13 were hepatomas. In male B6C3F1 controls, 23 tumors developed in 22/79 (28%) mice, 8 of which were hepatomas. The tumor incidence in B6C3F1 females was 13/18 (72%) (12 hepatomas) compared with 8/87 (9%) (0 hepatomas) in controls. In 13/17 (76%) B6AKF1 male survivors, 14 tumors were found (13 were hepatomas). In B6AKF1 male controls, 17 tumors (5 hepatomas) were found in 16/90 (18%) mice. The number of female B6AKF1 mice which developed tumors was 7/16 (44%), and 3/7 were hepatomas. In control mice of the same sex and strain, 9 tumors were found in 7/82 (9%) mice; one was a hepatoma [4].

Ethylene thiourea (ETU) is an impurity and degradation product of ethylenebisdithiocarbamic acid (EBDC) fungicides [184,185] including bis(2-hydroxyethyl)dithiocarbamic acid, potassium salt. ETU is also the principal product of the in vivo metabolism [186] and in vitro degradation [187-189] of EBDC fungicides. Crops sprayed with EBDC compounds have contained ETU in subsequent field studies [190-192]. Because ETU has induced cancer in mice and rats [4,193] and is a metabolite of EBDC fungicides, all EBDC fungicides should be handled as suspected carcinogens in the workplace. These include the calcium, diammonium, disodium (nabam), magnesium (maneb), potassium ammonium, and zinc (zineb) salts and all coordination products of these salts.

(iv) 2-(p-tert-Butylphenoxy)-isopropyl-2-chloroethyl Sulfite

The miticide 2-(p-tert-butylphenoxy)-isopropyl-2-chloroethyl sulfite was tested in mice and used as a positive control in a large screening study for NCI [4]. Groups of 18 male and 18 female B6C3F1 and B6AKF1 mice were administered 464 mg/kg 2-(p-tert-butylphenoxy)-isopropyl-2-chloroethyl sulfite by oral intubation from 7 to 28 days, followed by a diet of 1,112 ppm for 78 or 81 weeks. The number of hepatomas and the total number of mice observed with tumors were significant at levels of P=0.05 and P=0.01, respectively. Seven of the 16 B6C3F1 male survivors had tumors compared with 22/79 in male controls; 8/17 females of the same strain developed tumors as compared with 8/87 in female controls. Five out of 7 tumors in B6C3F1 males were

hepatomas, and 8/23 were hepatomas in male controls. One out of 8 tumcrs in female B6C3F1 mice was a hepatoma; no hepatomas were found in the controls. In the B6AKF1 strain, 2/17 males had tumors (one was a hepatoma), compared with 16/90 male controls (5 hepatcmas among 17 tumors). Four of the 16 female B6AKF1 survivors had tumors other than hepatomas. In B6AKF1 female controls, one hepatoma was found among 9 tumors in 7/82 mice [4].

The miticide was also tested in rats and dogs [194]. In rats fed 400 ppm, 7/90 (8%) developed tumors: 2 liver carcinomas and 5 bile duct adenomas. None of the 193 controls produced similar lesions. Dogs fed 500 or 828-1,420 ppm for 3.5 years were studied. All 14 animals surviving 811 or more days developed cancer of the biliary system while no tumors appeared in the controls [195]. The IARC has reviewed the literature on this compound and has concluded that it is an animal carcinogen [196].

(v) Captan

The fungicide captan was studied by NCI for carcinogenicity in rats and mice [197]. Both sexes of rats received dietary doses of 2,525 or 6,050 ppm. Both sexes of mice received 8,000 or 16,000 ppm. Thyroid and adrenal gland tumors were found in female rats; however, these endocrine tumors were believed to have been spontaneous and not related to treatment. In the treated mice, incidences of polypoid carcinoma of the duodenum were statistically significant both in male mice (P=C.C33), with incidences of 0/68 (0%) in the controls, 1/43 (2%) in the low- dose group, and 3/46 (7%) in the high-dose

group, and in female mice (P=0.022), with incidences of 0/68 (0%) in controls, 0/49 (0%) in the low-dose group, and 3/48 (6%) in the high-dose group. When the incidences of various adenomatous polyps were combined with those of polypoid carcinoma, the figures for male mice increased substantially in significance (P=0.008) 0/68 (0%) in the controls, 3/43 (7%) in the low-dose group, and 5/46 (11%) in the high-dose group. NCI concluded that under the conditions of this bioassay, tumors in the duodenum of mice were associated with administration of captan, but there was no convincing evidence that the tumors observed in rats were related to treatment [197].

(vi) Carbon Tetrachloride

NCI tested a group of male rats which received subcutaneous injections twice weekly of 1.3 ml/kg of a 50% solution of carbon tetrachloride in corn oil. Of these, 4/12 Wistar rats, 8/13 Osborne-Mendel rats, and 12/15 Japanese rats, which had survived 70 weeks or more, developed hepatocellular carcinomas. No tumors were induced in the 12 rats of each strain in the control group. It was concluded that carbon tetrachloride can induce carcinomas of the liver in rats [198]. NCI has also used carbon tetrachloride as a positive control chemical in bioassay testing [199].

Della Porta et al, in an NCI study [200], administered 30 weekly doses of 0.0625-0.125 ml/kg carbon tetrachloride to 10 male and 10 female hamsters by intubation. Liver-cell carcinomas developed in five animals of each sex that survived 10 or more weeks after the cessation of treatment. No controls were

reported.

As a result of a review of all available data on animal bioassays, NIOSH recommended that occupational exposure should be limited to 2 ppm as a ceiling based on a 1-hour sampling time and 45 liter sample, which should materially reduce the risk of cancer from occupational exposure to carbon tetrachloride [201].

(vii) Chloramben

In an NCI study [202], Osborne-Mendel rats and B6C3F1 mice received either 10,000 or 20,000 ppm of chloramben. The pathologists determined that chloramben did not induce tumors in the rats although some abnormal symptoms appeared. The incidence of hepatocellular carcinoma in both male mice [9/69 (13%) in controls, 16/48 (33%) in the low-dose group, and 14/48 (29%) in the high-dose group, $P<0.029$] and female mice [2/67 (30%) in controls, 7/48 (15%) in the low-dose group, and 10/50 (20%) in the high-dose group, $P=0.004$] was higher than that in the controls. However, spontaneous hepatocellular carcinoma is not uncommon in this strain of mouse, particularly in males. Therefore, the pathologists concluded that the hepatocellular carcinomas seen in treated male mice were not treatment related. However, it was also the pathologists' opinion that the tumor incidence in female mice had a significant relationship to the treatment with chloramben [202].

(viii) Chlordane

In an NCI bioassay [203], groups of 50 mice of each sex received chlordane in the diet in concentrations of 29.9 or 56.2 ppm (male), and 30.1 or 63.8 ppm (female).

Hepatccellular carcinoma showed a highly significant dose-related trend in mice. Incidence rates for males were: 2/18 (11%) in controls, 16/48 (33%) in the low-dose group, and 43/49 (88%) in the high-dose group ($P<0.001$). For females, the incidence rates were: 0/19 (0%) in the control group, 3/47 (6%) in the low-dose group, and 34/39 (88%) in the high-dose group ($P<0.0001$). EPA has concluded that chlordane is carcinogenic in mice and has restricted its usage based partially on that conclusion (Federal Register 41:7552-85, February 19, 1976).

(ix) Chlorobenzilate

Chlorobenzilate was tested by Bionetics Research Labs [4] in 18 male and 18 female B6C3F1 and B6AKF1 mice for NCI. The mice were given a single dose of 215 mg/kg chlorobenzilate by stomach tube at 7 days of age. When the animals were 4 weeks old, the compound was administered at 603 ppm in the diet for 83 weeks. Total tumor incidence and that of hepatoma were both increased significantly ($P=0.01$). In B6C3F1 mice, 11/17 males developed 13 tumors, 9 of which were hepatomas, compared with 22/79 control males with tumors, 8 of which were hepatomas. In females, 2/18 developed 2 nonhepatomatous tumors compared with 8 nonhepatomatous tumors in 8/87 controls. In B6AKF1 mice, 8/17 males developed 8 tumors, 7 of which were hepatomas. Among control males, 16/90 developed 17 tumors, 5 of which were hepatomas. In treated females, 3/18 developed 3 tumors but no hepatomas; in control females 7/82 developed 9 tumors, with 1 hepatoma [4].

In an NCI bioassay [204], chlorobenzilate was fed to B6C3F1

mice and Osborne-Mendel rats. Average levels in the diet were 4,231 and 7,846 ppm for male mice and 3,200 and 5,908 ppm for female mice, during the 78 weeks of feeding. Dosed mice had significantly higher incidences of hepatocellular carcinomas than did control mice: 4/19 (21%) in control males compared with 32/48 (67%) in low-dose males (P=0.001) and with 22/45 (49%) in high-dose males, (P=0.034); 0/20 (0%) in control females compared with 11/49 (22%) in low-dose females (P=0.016) and with 13/50 (26%) in high-dose females (P=0.007). Cortical adenomas in rats were discounted after comparison with historical controls [204].

(x) Chloroform

A study conducted by NCI [199] showed that chloroform administered by gavage produced liver tumors in B6C3F1 mice and kidney tumors in Osborne-Mendel rats. Groups of 50 male and 50 female mice (35 days old) were given two dose levels of chloroform in corn oil five times/week for 78 weeks and sacrificed after 92 to 93 weeks. The average dose levels were 138 and 277 mg/kg for males and 238 and 477 mg/kg for females. Except for a reduced survival in females given the higher dose, the survival was comparable for test and control groups. At the end of the experiment, 44/45 (98%) of the males and 39/41 (95%) of the females given the high dose had hepatocellular carcinomas; 18/50 (36%) of the males and 36/45 (80%) of the females at the lower dose developed liver carcinomas. For male controls, the liver tumor incidence was 1/18 (6%) while no tumors occurred in 20 female controls. The incidence of tumors in test animals was significantly different (P<0.001) from that in controls [199].

In this same study, groups of rats were started on test at 52 days of age. Two dose levels of chloroform were given by gavage for 78 weeks, and the animals were sacrificed 111 weeks after the start of the experiment. The dose levels for males were 90 and 180 mg/kg, and females were given average levels of 100 and 200 mg/kg. The kidney epithelial tumor incidence in male rats was significantly increased (P=0.0016) over controls. No tumors were observed in 99 controls; 4/50 (8%) and 12/50 (24%) were noted in low- and high-dose level test groups, respectively. A decreased survival rate was noted in all test rats [198]. NIOSH recommended that occupational exposure to chloroform should be limited to 2 ppm as a ceiling based on a 1-hour sampling time and 45 liter sample, which should materially reduce the risk of cancer from occupational exposure to chloroform [205].

(xi) DBCP

In 1972, the NCI undertook studies of the possible carcinogenicity of the fumigant DBCP [206]. The final report [206] revealed that male B6C3F1 mice received 160 or 80 mg/kg/day of DBCP by gavage for 11 weeks, 200 or 100 mg/kg/day for 14 weeks thereafter, and 260 or 130 mg/kg/day for an additional 22 or 33 weeks, respectively. The time-weighted average daily doses were 219 mg/kg for the high-dose group and 113 mg/kg for the low-dose group. The female mice of the same strain received 120 or 60 mg/kg/day during the first 11 weeks and thereafter received the same doses as the males. The time-weighted average doses for the females were 209 mg/kg and 109 mg/kg. Osborne-Mendel rats of both sexes were given

identical doses: 12 or 24 mg/kg for the first 9 weeks, 15 mg/kg for 69 weeks (males) or 64 weeks (females) thereafter for the low-dose rats, followed by a 5-week observation period for the low-dose group males, and 30 mg/kg for 55 weeks for the high-dose group. For both male and female rats, the time-weighted average daily doses, 5 days/ week, were 15 mg/kg for the low-dose group and 29 mg/kg for the high-dose one.

The incidences of squamous cell carcinoma of the stomach in male mice were 43/46 (93%) in the low-dose group and 47/49 (96%) in the high-dose group compared with 0/20 in controls ($P<0.001$). In female mice, squamous cell carcinomas of the stomach occurred in 0/20 (0%) controls, 50/50 (100%) low-dose animals, and 47/48 (98%) high-dose animals ($P<0.001$).

The incidences of stomach cancer in male rats were 0/20 (0%) in the control group, 47/50 (94%) in the low-dose group, and 47/50 (94%) in the high-dose group ($P<0.001$). In female rats, the incidences were 0/20 (0%) in the control group, 38/50 (76%) in the low-dose group, and 29/49 (59%) in the high-dose group ($P<0.001$). Adenocarcinoma of the breast appeared in 2/20 (10%) controls, 24/50 (48%) low-dose females, and 31/50 (62%) high-dose female rats ($P<0.001$).

Based on this study, OSHA has determined that DBCP poses a carcinogenic risk to workers. OSHA has promulgated a permanent standard for occupational exposure to DBCP that sets permissible exposure limits of 1 ppb as an 8-hour time-weighted average and 10 ppb as a ceiling (Federal Register 43:11514, March 17, 1978).

(xii) DDT, o,p'-DDD, and p,p'-DDD

After a thorough review of the available world literature, NIOSH has determined that DDT should be handled in the workplace as a suspected occupational carcinogen [31]. The DDT metabolites o,p'-DDD and p,p'-DDD have also caused cancer in mice [31]. In 1974, IARC also reviewed available literature and found that DDT caused liver cancer in mice [207]. Similarly, EPA concluded in 1975 that tumors were produced in mice experimentally exposed to DDT, and EPA restricted the usage of DDT based partially on that conclusion [208].

(xiii) EDB

The fumigant ethylene dibromide (EDB) was assayed for carcinogenicity in a study for NCI and preliminary results were published [209]. The final bioassay report is scheduled for publication in 1978. According to the preliminary results reported by Powers et al [209], EDB was given to rats at 80 or 40 mg/kg and to mice at 120 or 60 mg/kg by daily intubation for 54 or 62 weeks, except when toxicity forced the total discontinuation of administration or reduction of the maximum tolerated dose to that of one-half the maximum tolerated dose during the experiment. The tumors were squamous-cell carcinomas which originated in the forestomach, invaded locally, and metastasized throughout the abdominal cavity. In rats, an average of 83% of the males developed tumors vs 70% of the females, and tumor incidence was greater at the lower dose than at the higher dose at the termination of the experiment after 54 weeks (98 vs 68% in males and 82 vs 58% in females,

respectively). The control populations did not develop squamous-cell carcinomas of the stomach. The fraction of mice that developed squamous-cell carcinomas was 74% in males and 72% in females by the termination of the experiment at 90 weeks. The data from this single study indicate that EDB is a carcinogen after daily introduction of about one-half the maximum tolerated dose into the stomach of rats and mice for up to 62 weeks [209]. NIOSH has recommended a standard for occupational exposure to ethylene dibromide that would limit exposure to 1.0 mg/cu m as a ceiling based on a 15 minute sampling period [210].

(xiv) Heptachlor

Groups of 50 mice were administered heptachlor in feed. Time-weighted doses averaged 6.1 and 13.8 ppm for male mice and 9 and 18 ppm for female mice. Hepatocellular carcinoma showed a highly significant dose-related trend in males: in the control group 5/19 (26%), 11/46 (24%) in the low-dose group, and 34/47 (92%) in the high-dose group, ($P<0.001$) and in females: 2/10 (20%) in the control group, 3/47 (6%) in the low-dose group, and 30/42 (71%) in the high-dose group, ($P<0.0001$) [211]. Heptachlor was not significantly carcinogenic in rats. EPA has concluded that heptachlor is carcinogenic in mice (Federal Register 41:7552-85, February 19, 1976) and has restricted its use partially based on that conclusion.

(xv) Kepone

In an NCI bioassay study [85], Kepone was fed at average concentrations of 8 and 24 ppm to male rats,

18 and 26 ppm to female rats, 20 and 23 ppm to male mice, and 20 and 40 ppm to female mice. Clinical signs of toxicity were observed in both species, including generalized tremors and dermatologic changes. A significant increase ($P<.05$) was found in the incidence of hepatocellular carcinomas in high-dose level rats and in mice at both dose levels of Kepone. The incidences in the high-dose groups were 3/44 (7%) and 10/45 (22%) for male and female rats, compared with 0% in 105 and 100 controls, respectively, for both sexes; and 43/49 (88%) and 23/49 (47%) for male and female mice, compared with 8/49 (16%) and 0/40 (0%) for male and female controls. For the low-dose mice the incidences were 39/48 (81%) for males and 26/50 (52%) for females. Also, the length of time until detection of the first hepatocellular carcinoma observed at death was shorter for treated than control mice and appeared inversely related to the dose for both sexes and species [85]. NIOSH has recommended that the workplace environmental level for Kepone should be limited to 1 mg/cu m as a time-weighted average concentration [212].

(xvi) Mirex

In the screening test performed by Bionetics Research Labs and reported in 1968 [4], mirex was administered both orally and subcutaneously in two groups of 18 male and 18 female B6C3F1 and B6AKF1 mice. In the first study, 10 mg/kg mirex was fed to the animals by oral intubation from day 7 to day 28, after which the compound was administered in the diet at 26 ppm. Feeding was continued for 59 weeks in the male mice cf both strains and for 70 and 69 weeks in female B6C3F1 and

B6AKF1 mice, respectively. The number of mice that developed tumors was significant (P=0.01), and the occurrence of hepatomas was also significant (P=0.01) among the tumor types observed. Incidence in male B6C3F1 mice was 7/18 (39%; 6 were hepatomas) compared with 23 tumors in 22/79 (28%) controls (8 were hepatomas). In female mice of the same strain, incidence was 8/16 (50%; all hepatomas) compared with 8/87 (9%; no hepatomas) in controls. Six tumors, 5 of which were hepatomas, were observed in 5/15 (33%) male B6AKF1 mice, compared with 17 tumors (including 5 hepatomas) in 16/90 (18%) male controls. Tumor incidence in female B6AKF1 mice was 10/16 (62%; all were hepatomas). In corresponding controls, 9 tumors, one of which was a hepatoma, were found in 7/82 mice (9%) [4].

In the second test, the same number of male and female B6C3F1 and B6AKF1 mice received a subcutaneous injection of 1,000 mg/kg mirex on the 28th day; the experiment was terminated at the same time as the first study. The results showed that the total number of mice that developed tumors was statistically significant at P=0.01, and of the total tumors observed, reticulum cell sarcomas and hepatomas occurred at a significant level (P=0.01). In B6C3F1 male mice, 9 tumors were found in 8/18 (44%) mice (including 6 reticulum cell sarcomas and 2 hepatomas), compared with 31 tumors in 27/141 (19%) male controls (including 8 reticulum cell sarcomas and 9 hepatomas). Incidence in female B6C3F1 treated mice was 0/17 (0%) compared with 9/154 (6%; 1 reticulum cell sarcoma) in untreated females of the same strain. Seven tumors (including 1 reticulum cell sarcoma and 4 hepatomas)

were found in 6/17 (35%) treated B6AKF1 males; the incidence in controls was 8/161 (5%; including 1 hepatoma). In B6AKF1 female mice, 3 reticulum cell sarcomas and 1 hepatoma were among the 5/18 (28%) tumors observed. In female controls, 5 reticulum cell sarcomas were found among 18 tumors in 17/157 (11%) mice [4].

The hepatocarcinogenicity of mirex has been shown in rats at 50 and 100 ppm in a chronic feeding experiment reported by Ulland et al [5]. Liver lesions including neoplastic nodules and hepatocellular carcinomas were observed. In the 50 ppm group, 1/26 (4%) males and 0/26 (0%) females developed hepatocellular carcinomas. The incidences for the 100 ppm groups were 4/26 (15%) in males and 1/26 (4%) in females. While the incidence of hepatocellular carcinomas is not significantly increased compared with that of control animals, when neoplastic nodules are included, the incidence in high-dose males (7/26, 27%) is significantly different ($P<0.05$) from that in controls (0/20). Neither hepatic nodules nor hepatocellular carcinomas were observed in control rats [5].

(xvii) Nitrofen

The herbicide nitrofen was bioassayed for NCI [213] at time-weighted average doses of 2,300 and 3,656 ppm for male rats, 1,300 and 2,600 ppm for female rats, and 2,348 and 4,696 ppm for both male and female mice. The incidence of pancreatic carcinomas had a statistically significant ($P<0.001$) positive association with the concentration of nitrofen in the diet of female rats, 0/110 in the control group, 2/50 (4%) in the low-dose group, and 7/50 (14%) in the high-dose group. By week

45, 50% of high-dose males were dead. This prevented the evaluation of the carcinogenicity of nitrofen in male rats. In mice of both sexes, the incidence of hepatocellular carcinoma at both high- and low-dose levels was highly significant ($P<0.001$) when compared with the controls: 9/74 (12%) controls, 36/49 (73%) low dose, and 46/48 (96%) high dose, for males and 0/80 (0%) controls, 36/41 (88%) low dose, and 43/44 (98%) high dose, for females. The incidence of hemangiosarcoma had a statistically significant relationship with nitrofen concentration in the diet of high-dose male mice when compared with controls ($P=0.022$). Incidences of hemangiosarcoma in male mice were 0/74 (0%) controls, 1/44 (2%) low dose, and 4/48 (8%) high dose.

(xviii) 2-Nitropropane

Groups of Sprague-Dawley rats and New Zealand White rabbits were exposed to commercial grade 2-nitropropane in an inhalation study performed for NIOSH [214]. Fifty male rats and 15 male rabbits were exposed to 207 ppm 2-nitropropane for 7 hours/day, 5 days/week. A second group of identical composition was exposed to 27 ppm on the same schedule, and a third untreated group served as controls. Ten rats from each group were killed after exposure periods of 2 days, 10 days, 1 month, 3 months, and 6 months. Liver neoplasms, identified as hepatocellular carcinomas or hepatic adenomas, were observed in all 10 rats exposed to 207 ppm 2-nitropropane for 6 months. No tumors were observed in any other test or control rats or rabbits. However, in rats exposed to 207 ppm for 3 months,

hepatocellular hypertrophy, hyperplasia, and necrosis were observed. Rats exposed to 207 ppm 2-nitropropane for 1,3, and 6 months also showed increased liver weights [214].

In another inhalation study, five species of laboratory animals were exposed to acute and chronic levels of 2-nitropropane. Two animals of each species received treatment at the various exposure levels, which ranged from 9,000 ppm for 1 hour to 83 ppm for 26 weeks. Initial results showed nc histologic changes in monkeys, rabbits, guinea pigs, and rats exposed to 328 ppm, or less, for any period of time. Severe liver damage and slight to moderate heart and kidney damage were observed in two cats that died within 17 days of exposure to 328 ppm 2-nitropropane. A subsequent examination showed clear cell foci in two rats that had been exposed to concentrations of 300 ppm for 119 hours. These types of lesions were similar to those found in the above study and have been frequently observed in rats exposed to known hepatic carcinogens prior to the development of hepatocellular carcinomas [214].

While one animal study has indicated carcinogenicity of 2-nitropropane in rats, a complete evaluation has not been made. In light of this study, however, NIOSH believes that it would be prudent to handle 2-nitropropane as a suspected occupational carcinogen. NCI is currently bioassaying 2-nitropropane.

(xix) 1,1,2,2-Tetrachloroethane

An NCI bioassay of 1,1,2,2-tetrachloroethane [215] indicated that this compound is carcinogenic in mice. Groups of 50 male and 50 female B6C3F1

mice (35 days old) were given two dose levels of 1,1,2,2-tetrachloroethane in corn oil by gavage five times a week for 78 weeks and sacrificed after 90 weeks. The average levels were 142 and 282 mg/kg/day for both sexes. In males, hepatocellular carcinomas occurred in 3/36 (8%) in the control group, 13/50 (26%) in the low-dose group, and 44/49 (90%) in high-dose mice ($P<0.001$). In females, the same tumor was found in 1/40 (3%) in the control group, 30/48 (63%) in the low-dose group, and 43/47 (91%) in high-dose mice ($P<0.001$). While no statistically significant tumor rates occurred in rats and no conclusive evidence for carcinogenicity in rats was presented, 2 hepatocellular carcinomas and 1 neoplastic nodule (both rare in male rats) were found in 49 male rats, while none were found in control rats [215].

(xx) Tetrachloroethylene

A bioassay study by NCI [216] indicated that tetrachloroethylene is carcinogenic in mice. Male and female B6C3F1 mice in groups of 50 were administered tetrachloroethylene in corn oil by gavage 5 days/week for 78 weeks followed by observation for 12 additional weeks before sacrifice. Male mice received 536 or 1,072 mg/kg/day and females received 386 or 772 mg/kg/day. Hepatocellular carcinomas occurred in a significant number of both sexes. In males, the tumors were found in 2/20 (10%) control, 32/49 (65%) low-dose, and 27/49 (56%) high-dose mice ($P<0.001$). In females, the incidences were 0/20 (0%) control, 19/48 (40%) low-dose, and 19/48 (40%) high-dose mice ($P<0.001$). Rats dosed with 471-949

mg/kg/day experienced a high rate of early mortality, and consequently, tetrachloroethylene carcinogenicity could not be assessed [216].

(xxi) Tetrachlorvinphos

Using B6C3F1 mice and Osborne-Mendel rats in groups of 50 animals of each sex [217], tetrachlorvinphos was bioassayed by NCI for carcinogenicity. Mice were fed 8,000 or 16,000 ppm for 80 weeks and sacrificed after 92 weeks. Male mice developed a significant incidence of hepatocellular carciroma: 0/9 (0%) control, 36/50 (72%) low dose, and 40/50 (80%) high dose ($P<0.001$). Female mice experienced an increased incidence of neoplastic nodules: 1/48 (2%) control, 14/49 (29%) low dose ($P<0.001$), and 9/47 (19%) high dose ($P=0.007$). Rats received 4,250 or 8,500 ppm for 80 weeks with sacrifice after 111 weeks. Female rats developed C-cell adenoma of the thyroid in 1/46 (2%) in the control group, 2/50 (4%) in the low-dose group, and 7/46 (15%) in high-dose rats ($P=0.013$). Cortical adenoma of the adrenal was also significant in female rats: 0/50 (0%) in the control group, 2/49 (4%) in the low-dose group, and 5/50 (10%) in the high-dose group ($P=0.017$) [217].

(xxii) Trichloroethylene

Trichloroethylene was administered to rats and mice of both sexes by intubation 5 days/week at two dose levels for 78 weeks. Mice were necropsied after 90 weeks and rats after 110 weeks. Male mice receiving an average of 2,339 mg/kg/day had a 64% incidence of hepatocellular carcinomas ($P<0.001$) while those receiving an average of 1,169 mg/kg/day had

a 52% incidence (P=).004). In control males, 5% developed those tumors. Female mice receiving 1,739 mg/kg/day had a 23% incidence rate of hepatocellular carcinomas (P=0.008) while those at 869 mg/kg/day did not develop a significantly greater amount of tumors than controls. Rats did not develop any tumors at a significantly increased rate [218].

As a result of animal testing and metabolic similarity to such carcinogens as vinyl chloride, NIOSH has concluded that trichloroethylene has a carcinogenic potential in the workplace although not a particularly strong one [219]. NIOSH recommends that a level of 25 ppm can be uniformly achieved in industry by use of existing control technology and should be met. Worker exposure should continue to be reduced beyond this level as methodology develops.

(xxiii) Trifluralin

Trifluralin was assayed in another NCI study [220]. The average high and low dietary concentrations of the herbicide were 4,125 and 8,000 ppm for male rats, 4,125 and 7,917 ppm for female rats, 2,000 and 3,744 ppm for male mice, and 2,740 and 5,192 ppm for female mice. For female mice, the correlation between increased dosage and elevated incidence of hepatocellular carcinomas was significant (P<0.001), with incidences of 0/60 (0%) in controls, 12/47 (26%) in low-dose mice, and 21/44 (48%) in high-dose mice. Also significant was the relationship between dose and incidence of alveolar/bronchiolar adenomas in female mice, 0/59 (0%) in the controls, 6/43 (14%) in the low-dose group, and 3/30 (10%) in the high-dose group

(P=).036). Squamous-cell carcinomas of the stomach were observed in dosed female mice, but not in controls. Although incidences of these tumors were not statistically significant [0/60 (0%) in controls, 4/45 (9%) in the low- dose group, and 1/44 (2%) in the high-dose group] they are unusual lesions in B6C3F1 mice and were considered to be treatment related [220]. Significant evidence of carcinogenicity was not indicated in male mice and male and female rats.

(B) Pesticides for Which Available Test Data Are Inconclusive

The 27 pesticides discussed in this section have not yielded conclusive evidence to implicate them as cancer-suspect agents because of poor experimental design, lack of statistical analysis of the data, or conflicting data among separate studies. Also discussed in this section are certain compounds tested in the Bionetics Research Labs screening study performed for NCI and reported in 1968 [4]. Positive results reported for the compounds tested in that study but not supported by other confirming evidence are included below. Many of these compounds are now being bioassayed by NCI. Their test results are summarized in Table XIV-9. Additional well-desiqned experiments are recommended to develop the quality data necessary for their classification.

(i) Azobenzene

Groups of 18 male and 18 female B6C3F1 and B6AKF1 mice were administered 21.5 mg/kg azobenzene in 0.5% gelatin by stomach tube from days 7 to 28, after which the animals were fed 56 mg/kg azobenzene in the daily diet for 80 weeks. As reported by Bionetics Research Labs in 1968, incidence of hepatomas in treated male B6C3F1 mice was 8 tumors/18 mice compared with 8 tumors/79 controls, and in male B6AKF1 mice, the rates were 2/18 compared with 5/90 in controls (P=0.01). The incidence of hepatomas in female mice was similar to that in the controls [4].

(ii) Calcium Cyanamide

Calcium cyanamide was tested for NCI in 18 B6C3F1 and 18 B6AKF1 male and female mice and the results reported in 1968 [4]. The compound was administered at 100 mg/kg by oral intubation from days 7 to 28, after which it was mixed with the ground feed at 240 ppm until the mice were necropsied during week 82. Results showed that the occurrence of reticulum cell sarcomas was significant (P=0.01). Tumor incidence was 5 sarcomas/16 males and 3 sarcomas/18 females in B6C3F1 mice, compared with 5/79 and 4/87 for controls. In B6AKF1 mice, 2 hepatomas developed in 17 female mice and none were found in the 18 males necropsied, compared with 1/90 and 3/82 for male and female controls, respectively [4]. An NCI bioassay report is scheduled for release in 1978.

(iii) (2-Chloroethyl)triethyl-

ammcnium Chloride

In a study for NCI reported in 1968 [4], (2-chloroethyl)triethylammonium chloride (CCC) was tested on B6C3F1 and B6AKF1 mice. Eighteen male and female mice of each strain received 21.5 mg/kg CCC by oral intubation on days 7-28, after which the compound was mixed with the ground feed at 65 ppm for 82 weeks. The number of hepatomas found at necropsy was significant at a P=0.01 level. In B6C3F1 mice, 5 hepatomas occurred in 18 males and 0 hepatomas in 18 females, compared with 8 hepatomas/79 and 0/87 in controls, respectively. Five hepatcmas were found in 18 B6AKF1 male mice and 9 in 15 female mice that survived, compared with 5 hepatomas/90 and 1/82, respectively, in the control group [4].

(iv) Chloropicrin

Chloropicrin was tested by NCI in a bioassay study [221] using Osborne-Mendel rats and B6C3F1 mice. The compound was administered by gavage in corn oil 5 days/week during dosing periods. Because of early high mortality, rats were only dosed periodically during the study. Average doses for male rats were 25 or 26 mg/kg/day, and for female rats, they were 20 or 22 mg/kg/day. Mice were dosed at 33 or 66 mg/kg/day, 5 days/week for 78 weeks without interruption. All dosing of animals stopped at 78 weeks. Rats were observed for 32 more weeks and mice for 13 more weeks. The short survival time for rats did not permit an assessment of carcinogenicity for them.

While the mice did not have any statistically significant tumor incidences, two carcinomas and a papilloma did occur, which happened only rarely in historical controls. In summary, short survival of the rats prevented any carcinogenic effect in this species, and the mice did not demonstrate any significant tumor incidences [221].

(v) 2,4-D

In one carcinogenicity test, groups of male and female Osborne-Mendel rats were fed 2,4-D at rates of 0-1,250 mg/kg by Hansen et al [222]. The only statistically significant ($P<0.05$) increase in tumors (of no particular organ) occurred in high-dose males. The authors stated, "No target organ tumors were observed: the individual tumor types were randomly and widely distributed and of the type normally found in aging Osborne-Mendel rats....These tendencies do not reflect important pathologic differences."

In a study [4] for NCI, 2,4-D was tested in B6C3F1 and B6AKF1 mice. Only the isooctyl ester formulation significantly induced tumors. Eighteen male and 18 female mice of both strains received a subcutaneous injection of 2,4-D isooctyl ester at 21.5 mg/kg when 7 days of age. The observations continued through week 84 in the B6C3F1 strain and through weeks 86 and 81 in male B6AKF1 and female B6AKF1 mice, respectively. Results showed the total number of mice which developed tumors was significant ($P=0.01$), and the significant tumor type which occurred was reticulum cell sarcoma ($P=0.01$). In B6C3F1 males, tumor

incidence was 6/18 compared with 31 in 27/141 controls (3/18 reticulum cell sarcomas in treated vs 8/141 in untreated mice). Incidence was 2/18 in female B6C3F1 mice compared with 9/154 in control mice. Values for reticulum cell sarcomas were 0/18 in test and 1/154 in control mice of the same strain. In the B6AKF1 strain, the total number of mice which developed tumors was 2/18 in treated males and 8/161 in control males. The incidence of reticulum cell sarcomas was 0/18 and 0/161 in treated and untreated males, respectively. In B6AKF1 females, 6 tumors were found in 5/17 mice, 5 of which were reticulum cell sarcomas. In the B6AKF1 female controls, 18 tumors were found in 17/157 mice, 5 of which were reticulum cell sarcomas [4]. However, in another rat feeding study [223] and in a mouse feeding study [4] for NCI, significant tumor incidences were not observed when using 2,4-D and its isopropyl and butyl esters.

(vi) Dimethoate

Dimethoate, an OP insecticide, was given to rats orally at dose levels of 5-30 mg/kg and intramuscularly at 15 mg/kg. Malignancies developed in 9/71 orally treated rats: 2 malignant reticuloses, 4 spleen sarcomas, 1 colon sarcoma, and 2 liver carcinomas. In rats dosed intramuscularly, 6/30 rats developed cancer: 2 spleen sarcomas, 1 ovarian sarcoma, 1 unspecified sarcoma, 1 malignant reticulosis, and 1 liver carcinoma. Controls (36 oral, 35 intramuscular) developed no tumors. Mice topically administered dimethoate developed 4 leukoses and 1 mammary tumor (5/19

animals), but no controls were reported [224]. No probability statistics were presented. An NCI feeding study [225] tested dimethoate in rats and mice. Rats received average doses of 155 or 310 ppm (males) and 192 or 384 ppm (females). Mice were fed at rates of 250 or 500 ppm (both sexes). In spite of signs of typical dimethoate toxicity (tremors and hyperexcitability), low-dose rats and all treated mice survived long enough to allow an evaluation of carcinogenicity. No statistically significant increase in tumor incidence occurred in either sex or species. It was concluded that no carcinogenic effect resulted from dimethoate administration [225].

(vii) Dimethoxane

An experiment by Hoch-Ligeti et al [226] with dimethoxane administered as a 1% solution in the drinking water, a very large dose, resulted in the induction of malignant tumors, mostly hepatomas, in 14 of 25 male rats. One of 14 control animals developed cancer in the liver, kidney, spleen, and lungs. The small number of animals, the lack of experimental details, and the lack of statistical analysis for this single study do not provide a sufficient basis for a final conclusion.

(viii) 2,4-Dinitrotoluene

NCI [227] bioassayed 2,4-dinitrotoluene using groups of 50 Fischer 344 rats or 50 B6C3F1 mice of each sex. Dietary levels were 0.008 and 0.04% for mice and 0.008 and 0.02% for rats. Dosing occurred for 78 weeks followed by 13 additional weeks' observation for mice or 26 additional weeks'

observation for rats. While no malignant tumors developed at significant rates in rats, benign skin or subcutaneous fibromas did develop in 0/46 (0%) control, 7/49 (14%) low-dose, and 13/49 (27%) high-dose male rats (P=0.003), and benign mammary fibroadenomas occurred in 9/48 (19%) control, 12/49 (24%) low-dose, and 23/50 (46%) high-dose female rats (P=0.016). No tumors developed at significant rates in mice [227].

(ix) Diphenylacetonitrile

Eighteen male and female B6C3F1 and B6AKF1 mice were administered a single subcutaneous injection of diphenylacetonitrile at 464 mg/kg in a test performed for NCI by Bionetics Research Labs and reported in 1968 [4]. The mice were injected on day 28, and survivors were killed in week 77 of the study. The total number of tumors was significant (P=0.05), and of the total tumor types, reticulum cell sarcomas were significant at a level of P=0.01. Other tumor types were reported to be insignificant in occurrence. In B6C3F1 mice, 5/18 males developed tumors, 3 of which were sarcomas. Two reticulum cell sarcomas were present in the 3/16 female B6C3F1 mice which develcped tumors. Results for the B6C3F1 control group showed that 27/141 males developed 31 tumors, 8 of which were sarcomas, and that 9/154 females developed tumors, 1 of which was a sarcoma. In the B6AKF1 strain, 3/18 males developed tumors (1 was a sarcoma) compared with 8/161 control males (no sarcomas). Three out of 17 B6AKF1 female mice showed 4 tumors, 2 of which were reticulum cell sarcomas compared with 17/157 female control mice which developed 18 tumors, 5 of which were reticulum cell sarcomas [4].

(x) Endosulfan

Endosulfan was tested for NCI in 18 B6C3F1 and 18 B6AKF1 male and female mice by Bionetics Research Labs [4]. The two strains were administered 1.) mg/kg endosulfan by oral intubation on days 7-28, after which the compound was added to the ground feed at 3 ppm until the end of the study during week 77. Necropsies showed that the total number of tumors was significant (P=).05). Tumors developed in 5/14 male and 3/10 female B6C3F1 mice, compared with 23 tumors in 22/79 male and 8 tumors in 87 female control mice. In strain B6AKF1, 6 tumors developed in 5/16 males and 3 in 16 females, compared with 17 tumors in 16/90 males and 9 tumors in 7/82 females in the control group. Pulmonary adenomas were also significant at P=0.05. Tumor occurrence of this type in B6C3F1 mice was 2 tumors/14 males and 1 tumor/10 females, compared with 5/79 males and 3/87 females in the control group. In the B6AKF1 strain, 4 pulmonary adenomas were found in 16 male mice and 1 in 16 female mice; values for B6AKF1 controls were 9 tumors/90 males and 3/82 females [4].

In a recent NCI bioassay [228], endosulfan was fed to rats at 223-952 ppm and to mice at 2.0-6.9 ppm. High early mortality occurred for male rats and mice, and no conclusions about carcinogenicity could be made for them. Endosulfan was not found to be carcinogenic for female rats and mice.

(xi) Endrin

Treon et al [229] tested endrin in 6 groups of 20 male and 20 female Carworth rats. A diet of 0, 1,

5, 25, 50, or 100 ppm endrin was administered for 2 years. Survivors at 80 weeks included 12/80 rats given 50 or 100 ppm, 23/40 given 25 ppm, 28/40 given 5 ppm, 31/40 given 1 ppm, and 28/40 in the control group. The incidence of neoplasms in treated rats was no greater than that among controls.

The tumorigenicity of endrin was tested in Osborne-Mendel rats by Deichmann et al [230]. Diets containing 2, 6, or 12 ppm endrin (technical grade 98%) were administered to 50 male and 50 female rats for lifespan. The mean survival time in endrin-treated rats ranged between 17.6 months in males given 12 ppm to 20.8 months in females given 2 ppm. The mean survival time in a control group was 19.7 months for male rats and 19.5 months for female rats. The proportion of tumor-bearing rats and the incidence of mammary tumors, lymphomas, and other tumors were similar in treated and control rats. No liver-cell tumors were reported. Endrin is being tested by NCI and results are scheduled for release in 1978.

(xii) Ethylan

As reported in the 1968 Bionetics study [4] for NCI, 18 male and 18 female B6C3F1 and B6AKF1 mice received 215 mg/kg ethylan by oral intubation. The mice were administered the compound in this manner from days 7 to 28, after which 815 ppm ethylan was mixed with the ground feed for the duration of the experiment. The number of hepatomas found at necropsy (during week 84 for both B6C3F1 sexes, during week 86 for B6AKF1 male, and during week 87 for B6AKF1 female mice) was significant at a level of P=0.01. Seven hepatomas were found in

16 treated B6C3F1 male mice, and 1 hepatoma was found in 17 treated B6C3F1 female mice, compared with 8 hepatomas/79 male and 0/87 female control animals of the same strain, respectively. In treated B6AKF1 mice, 1 hepatoma was found in both groups of 18 male and female mice necropsied, compared with 5/90 male and 1/82 female control mice [4].

(xiii) Ethylene Oxide

Eighty-six inbred female Swiss-Webster mice were exposed inadvertently to ethylene-oxide-treated ground corncob bedding for 150 days in an experiment not designed to study the effects of ethylene oxide. The mice lived in untreated bedding for their lifetime (a maximum of 900 days) following exposure. Tumors developed at various sites in 63 exposed mice; no tumors were reported in 83 female mice 100-600 days old, which were not exposed to treated bedding [231]. This "study" was not designed for the purpose reported here and few conclusions can be drawn from it.

No skin tumors were observed on 30 female 8-week-old ICR/Ha Swiss mice which had been painted with 0.1 ml of a 10% solution of ethylene oxide in acetone three times/week for life. The average length of survival was 493 days [232].

Negative results were also obtained in a study by Walpole [233]. Twelve rats were subcutaneously injected with 1 g/kg ethylene oxide in arachis oil for 94 days on a unspecified schedule. No sarcomas were observed throughout the animals' lifetimes.

Ethylene oxide has produced genetic defects in a variety of

test systems (see Table XIV-10). The most likely mechanism for the production of these defects (mutations) is the alkylation of cellular constituents, including deoxyribonucleic acid (DNA). Such reactions have been observed with both proteins and nucleic acids, and the resulting molecules could very likely possess abnormal functional properties in the living organism [234].

While limited animal tests have not clearly indicated carcinogenicity, the alkylating and mutagenic properties of ethylene oxide are sufficient bases for concern, and NIOSH has recommended that workers should not be exposed at concentrations greater than a 135 mg/cu m (75 ppm) ceiling determined during a 15 minute sampling period and a 90 mg/cu m (50 ppm) TWA for up to a 10-hour day or 40-hour workweek.

(xiv) HCCH (Technical BHC)

HCCH typically contains the following isomers of hexachlorocyclohexane: 55-70% alpha, 6-8% beta, 10-18% gamma, 3-4% delta, and a small amount of epsilon. Nagasaki and coworkers [235,236] found that HCCH produced hepatomas in 20/20 male mice fed 600 ppm but none at lower levels. No tumors developed in control mice. However, Goto et al [237] found liver nodules but no definite cancers in male mice receiving 600 ppm HCCH in their diet for 26 weeks. Similarly, Fitzhugh et al [238] did not find an excess of tumors in rats fed 10, 50, 100, and 800 ppm HCCH. No statistical analyses of the data were given.

(xv) IPC and CIPC

Van Esch et al [239] studied the

effect of isopropyl phenylcarbamate (IPC) and isopropyl chlorophenylcarbamate (CIPC) as tumor initiators on Swiss mice in conjunction with the promoters croton oil and Tween 60. IPC and CIPC were administered as a single 15 mg dose once by intubation, as 10 weekly 15 mg doses by intubation, or in the diet at 0.1% for 6 months. Five percent croton oil was applied dermally two times/week, and Tween 60 was applied six times/week, both for 6 months. IPC applied 10 times with croton oil produced significantly more tumors (papillomas) than croton oil by itself ($P<0.05$). No other IPC combinations produced results significantly different from controls. A single application of CIPC with croton oil resulted in a significant increase in the papilloma incidence in females ($P<0.05$). No other CIPC combinations were significant. The authors stated that IPC and CIPC have weak initiating activity; however, while indicating cancer initiation, this study does not show that the substances were carcinogenic, and further testing is recommended by NIOSH.

(xvi) Lindane (gamma-HCCH)

Carcinogenic studies of lindane have shown both negative and positive results. It was determined not to be carcinogenic in the NCI bioassay study in rats and mice [240]. Negative results were also reported by Nagasaki et al [241] for male mice fed 100-500 ppm lindane, and by Fitzhugh et al [238] for male and female rats fed 5-1,600 ppm. Positive results occurred in a study by Thorpe and Walker [242] with a 96% incidence of liver tumors in male mice fed 400 ppm lindane compared with 24% in controls ($P<0.05$), and with a 95% incidence

in treated females compared with 23% in controls ($P<0.01$). A study by Goto et al [237] showed liver nodules in male mice examined after 26 weeks on a 300 ppm lindane diet.

(xvii) Mexacarbate

Mexacarbate was tested on male and female B6C3F1 and B6AKF1 mice for NCI. Mexacarbate was administered to 18 animals of each sex and strain by oral intubation at a dose of 4.64 mg/kg on days 7-28, after which the compound was mixed with the ground feed at 11 ppm. Necropsies in week 81 showed that the formation of hepatomas was significant at $P=0.05$. Tumor incidence in B6C3F1 mice was 5 hepatomas/16 in males and 0 hepatomas/17 in females compared with 8/79 and 0/87, respectively, in the controls. In B6AKF1 mice, incidence of hepatomas was 2 tumors/17 and 0/17 in male and female mice, respectively, and 5/90 and 1/82 in the control mice [4]. A bioassay report by NCI is scheduled for release in 1978.

(xviii) PCNB

Pentachloronitrobenzene (PCNB) was also tested by Bionetics Research Labs for NCI [4]. Eighteen male and 18 female B6C3F1 and B6AKF1 mice were given single doses of 464 mg/kg PCNB by oral intubation when the animals were 7 days of age. The same amount was given daily until the mice were 4 weeks old, when they were administered a diet containing 1,206 ppm PCNB. The experiment lasted 78 weeks. The number of mice observed with all types of tumors was statistically significant ($P=0.01$), and hepatomas occurred at the same level of significance. Six tumors, including 2 hepatomas, developed in

5/18 (28%) B6C3F1 male mice compared with 23 tumors, including 8 hepatomas in 22/79 (28%) male controls. Tumor incidence in B6C3F1 females was 5/18 (28%) compared to 8/87 (9%) in female controls (4 were hepatomas in treated mice and no hepatomas were found in controls). Eleven B6AKF1 male mice out of 17 (65%) developed 13 tumors (10 were hepatomas); 17 tumors were found in 16/90 (18%) male controls, including 5 hepatomas. Two tumors, 1 of which was a hepatoma, were found in 2/17 (12%) female B6AKF1 mice compared with 9 tumors, 1 of which was a hepatoma, in 7/82 (9%) female controls. Incidences of other tumors were similar in treated and control animals [4].

A bioassay study [243] conducted by NCI, however, has not found indications of carcinogenicity. In this study, mice or rats were fed PCNB in the diet at levels up to 14,635 ppm. These groups of 50 animals each showed no rare or unusual tumors. No statistically significant positive associations between PCNB and incidence of neoplasms were shown for any test group [243].

(xix) Piperonyl Butoxide

The occurrence of reticulum cell sarcomas was shown to be significant at a probability level of P=0.05 in male and female B6C3F1 and B6AKF1 mice orally administered piperonyl butoxide in a test for NCI by Bionetics Research Labs [4]. Eighteen mice of each sex and strain received a 100 mg/kg dose of the compound by oral intubation on days 7-28, after which the compound was mixed with the ground feed at 300 ppm for the remainder of the study. Results from the necropsies performed in week 83 showed reticulum cell sarcoma occurrence at

a rate of 5 tumors/15 male and 2/18 female B6C3F1 mice, compared with 5/79 and 4/87 in male and female controls, respectively. In B6AKF1 mice, reticulum cell sarcomas numbered 0 in 18 males and 1 in 18 females, respectively, compared with 1/90 and 3/82 in controls [4]. A bioassay report by NCI is scheduled for release in 1978.

(xx) Piperonyl Sulfoxide

Piperonyl sulfoxide was tested by Bionetics Research Labs for NCI [4] on groups of 18 male and female B6C3F1 and B6AKF1 mice. The two strains received a 46.4 mg/kg subcutaneous injection of the compound on day 28. Reticulum cell sarcomas were shown to occur at a significant level (P=0.05) in both male and female B6C3F1 mice, necropsied during week 71 and week 72, respectively. Male and female B6AKF1 mice were killed in weeks 83 and 84 of the experiment, respectively, and showed the same extent of reticulum cell sarcoma formation. Tumor occurrence was 1 sarcoma/18 mice for both male and female B6C3F1 mice, compared with 8/141 and 1/154 in controls. In B6AKF1 mice, sarcomas were found in 1/18 and 3/18 male and female mice vs)/161 and 5/157 for controls of the same strain. The development of reticulum cell sarcomas was also shown to be significant (P=0.01) in an oral test using the two strains of mice. Piperonyl sulfoxide was administered at 46.4 mg/kg by oral intubation on days 7-28, after which it was mixed with the ground feed at 111 ppm until the experiment was terminated during the same weeks cited above. Reticulum cell sarcomas were found at a rate of 8/18 and 1/18 in male and female

B6C3F1 mice, respectively, vs 5/79 and 4/87 in controls. In B6AKF1 mice, no tumors were found in the 18 males necropsied (1/90 for male controls), and 2 sarcomas were found in 17 female mice (3/82 for female controls) [4]. A bioassay report by NCI is scheduled for release in 1978.

(xxi) Sodium N,N-dimethyldithiocarbamate

Bionetics Research Labs [4] tested sodium N,N-dimethyldithiocarbamate (SDDC) in B6C3F1 and B6AKF1 mice. Eighteen male and female mice in each strain were administered 215 mg/kg SDDC by oral intubation on days 7 to 28, after which the compound was mixed with the ground feed at 692 ppm for the duration of the 78-week study. The total number of tumors was reported to be significant (P=0.05), and of the types of tumors found, pulmonary adenomas and hepatomas occurred at a significant level (P=0.05). In the B6C3F1 mice, 10/17 males had 11 tumors (including 3 pulmonary adenomas and 7 hepatomas). Twenty-two B6C3F1 male control mice of the 79 necropsied had 23 tumors (including 5 pulmonary adenomas and 8 hepatomas). Incidence in B6C3F1 control female mice was 8 tumors/87 mice, 3 of which were pulmonary adenomas. Six tumors occurred in 18 male B6AKF1 mice, 5 of which were pulmonary adenomas and none were hepatomas. In the male control group of this strain, 17 tumors (including 9 pulmonary adenomas and 5 hepatomas) were found in 16/90 mice. Two out of 18 female B6AKF1 mice had tumors, 1 of which was a pulmonary adenoma. In the B6AKF1 control group, 9 tumors (3 pulmonary adenomas and 1 hepatoma) were found in 7/82

female mice [4]. An NCI bioassay report is scheduled for release in 1978.

(xxii) Strobane

In the Bionetics study [4] performed for NCI, strobane was tested in male and female B6C3F1 and B6AKF1 mice. Eighteen mice of each sex and strain received 4.64 mg/kg strobane by oral intubation from day 7 to day 28, after which the compound was administered at 11 ppm in the ground feed for 80 weeks. Significant results included the total number of mice that developed tumors (P=0.01) and the incidences of hepatomas (P=0.01) and of reticulum cell sarcomas (P=0.05). Eight out of 15 (53%) male B6C3F1 mice developed tumors; 2 were hepatomas and 5 were reticulum cell sacromas. In the corresponding control group, 23 tumors were found in 22/79 (28%) mice; 8 were hepatomas and 5 were reticulum cell sarcomas. Tumor incidence in female B6C3F1 mice was 3/18 (17%) compared with 8/87 (9%) in controls; incidence of hepatomas was 0/18 (0%) and 0/87 (0%) and of reticulum cell sarcomas was 2/18 (11%) and 4/87 (5%) in female B6C3F1 treated and untreated mice, respectively. Eleven out of 18 (61%) male B6AKF1 mice developed tumors, all of which were hepatomas. In corresponding control mice, 17 tumors were found in 16/90 (84%) mice, 5 of which were hepatomas and 1 of which was a reticulum cell sarcoma. No tumors of any type were found in female B6AKF1 mice. Values for controls were 9 tumors, 1 of which was a hepatoma and 3 of which were reticulum cell sarcomas, in 7/82 (9%) female mice [4]. The IARC review of literature discussed only the Bionetics study [244].

(xxiii) 2,4,5-T

Mice were given drinking water containing 100 mg 2,4,5-T/l ad libitum for 2 months followed by 80 ppm of 2,4,5-T in the diet until death. Females showed a significant difference ($P<0.03$) in tumor rates, namely 13/25 (52%) for treated animals vs 9/44 (20%) for controls; neither males of this strain nor mice of another strain showed significant differences [245]. In the Bionetics Research Labs study [4], mice fed 2,4,5-T did not develop cancer to any significant extent; subcutaneous injection was likewise ineffective [4].

(xxiv) Thiourea

Thiourea was administered in varying concentrations in the diet to groups of 18 Osborne-Mendel rats for 104 weeks; 14 of the 29 survivors developed hepatic cell adenomas [246]. Tumor incidence was 3/5 (100 ppm), 4/8 (250 ppm), 2/8 (500 ppm), and 5/8 (1,000 ppm). Rats receiving a 2,500 ppm diet did not survive for more than 17 weeks. Untreated rats surviving 2 years showed a 1% spontaneous incidence of hepatic cell adenomas. Too few animals survived to provide adequate interpretation, and no statistical analysis was performed.

A 10% thiourea solution was administered intraperitoneally to a group of 12 rats 3 days/week for 6 months [247]. This group contained an unspecified number of each sex. On the 1st day, 3 ml were injected, 4 ml on the 2nd day, and 4 ml on the 3rd day of each week. The rats received a 0.2% solution of thiourea in the drinking water following the initial treatment. Five out of six

rats surviving 12-16 months developed tumors involving the area between the ear duct and the orbit, compared with no tumor development in the controls. Three of the tumors were diagnosed as squamous cell carcinomas, one a mixed sarcoma and squamous cell carcinoma, and one a mixed-cell sarcoma.

Of 42 newborn ICR Swiss mice administered a single subcutaneous injection of 2,500 mg/kg thiourea, no increase in the number of lung adenomas was observed compared with controls in mice killed 6 months after injection [248].

In another study [249], 0.2% thiourea was administered in the drinking water of 19 male albino rats for up to 26 months. One rat developed a myxomatous tumor of the nose and another developed epidermoid carcinomas in the area of the ear duct and the orbit. No tumors occurred in 12 control rats observed for 104 weeks. A significant increase in tumors was not demonstrated.

While design and analysis are inadequate for some of these studies and results are contradictory, some carcinogenicity may be indicated and further test data are necessary.

(xxv) Trichlorfon

In a study by Gibel et al [224], trichlorfon, a chlorinated OP pesticide, was tested orally and intramuscularly in rats and topically (dose not given) in mice. The rats were given total doses of 15 mg/kg by mouth and injections of 15 mg/kg. These groups had 7 malignant tumors in 28 animals treated orally (including 1 lung carcinoma, 1 malignant reticulosis, 2 spleen sarcomas, 1 liver carcinoma, 1

maxillary carcinoma, and 1 forestomach cancer in situ) and 4 malignant tumors in 27 injected animals (including 1 malignant reticulosis, 1 liver sarcoma, and 2 spleen sarcomas). No control rats (36 oral, 35 im) developed cancer, but no probability statistics were presented. Five of 14 mice developed myeloid leukosis. No control mice were reported and no probability statistics were presented [224]. NCI has tentatively selected trichlorfon for bioassay testing.

(xxvi) 2,4,6-Trichlorophenol

Bionetics Research Lab [4] tested 2,4,6-trichlorophenol in B6C3F1 and B6AKF1 male and female mice for NCI. Eighteen mice of each sex and strain were administered the compound at 100 mg/kg by oral intubation on days 7-28, after which it was mixed with the ground feed at 260 ppm for the duration of the 83-week experiment. The total number of tumors was significant at a level of P=0.01. Reticulum cell sarcomas and hepatomas were determined to be significant (P=0.05 among the tumor types found. In B6C3F1 mice, 9/18 males developed 10 tumors, 4 of which were reticulum cell sarcomas and 3 of which were hepatomas. In the control group, 23 tumors (including 5 sarcomas and 8 hepatomas) were found in 22/79 male mice. Seven out of 18 female B6C3F1 mice developed 8 tumors in all; 2 were sarcomas and 2 were hepatomas. In the control group, 4 of 8 tumors found in 87 females were sarcomas and no hepatomas were reported. Total tumors in 3/17 B6AKF1 male mice numbered 4, and 1 was a hepatoma. Values for controls were 1 sarcoma and 5 hepatomas out of 17 total tumors counted in 16/90 male mice. Of

the 2 tumors found in 17 female B6AKF1 mice, 1 was a sarcoma and 1 was a hepatoma. In the control group, 3 sarcomas and 1 hepatoma were found in a total of 9 tumors in 7/82 female mice. Other tumor types not included in the totals were insignificant in occurrence [4].

(C) Pesticides for Which Test Results Were Not Positive

The administration of picloram, dichlorvos, methyl chloroform, methoxychlor, and malathion to rats and mice showed no clear evidence of association with tumor incidence in NCI bioassay tests. Male and female mice and male rats fed picloram did not develop tumors significantly associated with the pesticide. Although female rats did develop hepatic nodules, they were benign [250]. A few tumors developed in mice fed dichlorvos, but there was not sufficient evidence to indicate that the tumors resulted from dichlorvos treatment [251]. Results for methyl chloroform were considered negative due to the high mortality and the similarity of tumors in control and in treated animals [252]. Tumor incidences for mice and rats administered malathion were not significantly different from incidence in controls. No tumors were judged to be related to malathion [253]. No significant tumor rates occurred for mice or rats of either sex in a bioassay of methoxychlor [254]. Fifty-five additional pesticides tested by Bionetics Research Labs for NCI [4] did have significant effects. These are listed in Table XIV-11.

It should be noted that relatively few of the

approximately 1,500 registered pesticides have been adequately tested for carcinogenicity, and very little is known about the carcinogenic risk of many of these substances. Accordingly, there is an obvious need for testing many registered pesticides for carcinogenic potential.

(2) Mutagenesis

In recent years, there has been a heightened interest in mutagenesis and related research. This interest has occurred for principally two reasons: (1) to assess the possibility that chemical substances may be producing genetic mutations which might alter the hereditary characteristics of humans [255], and (2) to use mutagenic assays as rapid and inexpensive surrogate methods to detect and to evaluate chemicals for potential carcinogenic effects [256]. The rationale for the latter lies in the prevailing theory that cancer is the result of a somatic mutation. The result of this interest has been the development of a large variety of experimental tests for mutagenesis utilizing bacteria, Drosophila, and various mammalian species [257-261].

The ubiquity of pesticides in the general and occupational environment has increased their importance as candidates for mutagen testing; however, the testing systems are varied, complex, and not easily correlated to human response. DDT has been most extensively studied in this regard [255] and the tests have yielded a mixture of positive and negative findings. DDT and its metabolite, DDE, have been consistently negative in bacterial assays. However, DDT and DDE have caused chromosomal

breaks and gaps in a number of in vivo and in vitro experiments. The occurrence of chromosomal damage in these experiments may correlate with the positive findings of similar chromosomal damage in occupationally exposed workers [255]. In the study by Rabello et al [255], 30 workers with high plasma DDT levels (average 0.993 mg/ml) were compared with 20 controls (average 0.275 mg/ml), and chromatid aberrations were found in 12% of the examined cells from the exposed group and in 8.8% of the examined cells of controls ($P<0.05$). Aldrin and dieldrin also caused chromosomal damage in mammalian cells in vivo and in vitro, yet they consistently produced negative results in bacterial reversion assays. Other pesticides which produce mutagenic effects in various organisms are shown in Table XIV-10. The ability of these pesticides to induce mutations in a wide variety of test systems is suggestive of their potential to induce mutations in human populations, but there is no evidence available to enable an adequate assessment of the quantitative aspects of relative risks for human populations. While the exact mechanisms and mutagenic potentialities cannot be stated with certainty, alkylating pesticides are most suspect of altering human genetic material. For example, ethylene dibromide is a bifunctional alkylating agent, and the most likely mode of mutagenic activity is the covalent bonding of ethylene dibromide to DNA. It must be realized, however, that there is no evidence to indicate that pesticides or any other organic compounds actually have caused mutagenesis in humans. For this reason, NIOSH does not recommend at this time that any pesticide be

controlled because of mutagenicity demonstrated in a test system.

While mutagenicity studies may not demonstrate toxicologic effects as dramatically as acute toxicity and carcinogenicity studies, they are nevertheless important. These studies show that genetic material is affected, and it is only prudent to avoid or greatly minimize exposure to material capable of such effects.

(3) Teratogenesis

The effects from the drug thalidomide have clearly shown that there is a potential for chemical substances to produce profound teratogenic abnormalities in humans. Since that finding, many tests have been conducted to determine the teratogenicity of chemicals in laboratory animals such as mice, rats, and hamsters. However, many of these tests have results from which it is difficult to draw conclusions regarding the teratogenicity of the compound due to the small sample size and to the lack of reporting numerical values or experimental methods critical to the findings. Pesticides, as a group, have been no exception. A summary of pesticides reported in the literature and labeled by the authors as being teratogenic, having teratogenic effects, or producing terata, appear in Table XIV-12.

Of the 15 pesticides listed , 8 of them (thiram, aldrin, dieldrin, endrin, folpet, captan, captafol, and 2,4,5-T) have sufficient data to indicate that these might pose a potential problem in humans.

Based on available evidence, four pesticides (parathion, dichlorvos, diazinon, and phosmet) tested in a small number of

animals, can be considered to be possibly teratogenic and should be handled with caution by women of childbearing age.

For the remaining three pesticides tested (diquat, paraquat, and trichlorfon), there is insufficient evidence to label these compounds as teratogens or possible teratogens.

The pesticides listed in Table XIV-12 can be grouped into OP, CC, dipyridyl, dithiocarbamate, phthalimide derivatives, and 2,4,5-T.

(A) Organophosphorus Compounds

The teratogenic potential of the OP compounds parathion, dichlorvos, and diazinon, among others, were studied using the Sherman rat fetus [262]. The highest nonfatal dose for each compound was: parathion, 3.5 mg/kg; dichlorvos, 15 mg/kg; diazinon, 100 and 200 mg/kg. Each dose was injected intraperitoneally for each compound on the 11th day after insemination. On the 20th day of gestation, the fetuses were removed for examination. Toxic levels of parathion and diazinon caused a high incidence of resorptions and reduced fetal weight. Parathion, dichlorvos, and diazinon produced various malformations: 1/28 fetuses exposed to 3.5 mg/kg parathion were edematous, 3/41 exposed to 15 mg/kg dichlorvos were omphalocelic (intestine herniated through umbilicus), 1/6 of those exposed to 200 mg/kg diazinon were hydrocephalic (cranial vault enlarged), 1/6 were missing the first distal phalanx, 1/6 were ectromelic (marked shortening or absence of long bones), and 6/30 exposed to 100 mg/kg diazinon had a dilated renal pelvis. The authors concluded that these three compounds were slightly teratogenic

[262]. After reviewing additional information on parathion, NIOSH concluded that parathion is not an active teratogen [89].

Two additional OP pesticides, trichlorfon and phosmet, have been labeled by Martson and Voronina [263] as having embryotoxic and teratogenic effects. These compounds were administered orally to groups of pregnant Wistar rats on days 9 or 13 of gestation, and daily or every other day throughout gestation. An 80 mg/kg dose of trichlorfon on day 9 resulted in an insignificant increase in embryo deaths. However, the same dose when given on day 13 resulted in a decrease in the number of developing fetuses, although corpora lutea production matched that of the controls. Post-implantation mortality in trichlorfon-treated animals increased significantly, and examination of dead fetuses revealed general edema and abnormalities such as exencephaly and "nonclosing eyelid" symptom. Trichlorfon administered at a dose of 8 mg/kg/day throughout gestation failed to show any significant deviation in embryogenesis. Analysis of embryoskeletal systems revealed only a few cases of wavy ribs. Trichlorfon administered in a dose of 1.5 mg/kg every other day throughout pregnancy resulted in a statistically verifiable reduction in the number of live fetuses. Hydrocephaly and subcutaneous hemorrhages were also seen. At a dose of 0.06 mg/kg given on alternate days, trichlorfon produced no adverse effects.

A 30 mg/kg dose of phosmet on day 9 resulted in malformations such as hypognathia and dislocation of extremities, but an insignificant increase in post-implantation mortality was

seen [263]. A 30 mg/kg dose of phosmet when administered on day 13 had no effect on embryo mortality before or after implantation. Examination of these embryos did reveal hydrocephaly in 33 of the 55 embryos studied.

(B) Organochlorine Compounds

The teratogenic potential of aldrin, dieldrin, and endrin was studied in 221 pregnant Syrian golden hamsters and in 50 pregnant CD1 mice [264]. These pesticides were given by oral intubation on days 7, 8, or 9 of gestation to hamsters and on the 9th day of gestation to mice, in doses equivalent to half the oral LD50 of each substance for both species. The abnormalities produced in both species included soft-tissue malformations, while the most frequent were cleft lip, webbed foot, and open eye. The latter two often occurred in combination with low fetal weight, indicating simply a suggestion of growth retardation. In hamsters, 62% of the 216 abnormal fetuses had only one abnormality, 23% had two abnormalities, and 15% had three or more. Also in this species, fused ribs occurred as a single defect, whereas 40-50% of cleft lip, cleft palate, open eye, and 87% of webbed feet occurred in combination with one or more other defects. The incidence of open eye, webbed foot, and cleft palate was uniform for all three pesticides in hamsters; however, in mice, different abnormalities were associated with each pesticide. Open eye and webbed foot were more frequent for aldrin in mice; dieldrin was associated with cleft palate and webbed foot. In both species, cleft palate, cleft lip, and fused ribs occurred significantly as a single

malformation, an indication of the teratogenicity of these pesticides [264].

(C) Dithiocarbamate Compounds

Thiram, dissolved in dimethylsulfoxide (DMSO) or carboxymethylcellulose (CMC) and administered to hamsters, was teratogenic in the hamster [265]. When DMSO was used, incidence of terata varied from 0/22 fetuses at 125 mg/kg to 11/48 (23%) at 31 mg/kg and to 6/6 (100%) at 250 mg/kg; controls had 27/149 (18%). In CMC, incidence progressed from 2 terata/68 fetuses (3%) at 125 mg/kg to 10/49 (20%) at 250 mg/kg to 5/15 (33%) at 300 mg/kg; controls had 3/714 (0.4%) [265]. Defects found with both solvents included head and limb abnormalities, fused ribs, maxillary or mandibular shortening, and umbilical hernia.

(D) Dipyridyl Compounds

Khera and Whitta [266] summarized the effects of paraquat and diquat in rats and found that a single 7 mg/kg injection of diquat on days 6-15 of gestation produced retarded growth of the sternum and auditory ossicles. Paraquat at 6.5 mg/kg on day 6 produced costal cartilage malformations. The number of animals tested and the incidence of malformations were not reported. Higher doses of both compounds caused increased abortion rates and, for diquat, more pronounced embryonic defects.

(E) Phthalimide Derivatives

Robens [267] found the following compounds to be teratogenic in hamsters: captan (300 mg/kg), folpet (500 mg/kg), and captafol (200 mg/kg); they were studied because of

their relationship to thalidomide. The compounds were administered orally in CMC to hamsters at a constant volume of 1 ml/100 g body weight. Administration was between days 6 and 10 of gestation with fetuses examined on day 15. Controls had 4 terata/1,081 fetuses (0.4%). At 300 mg/kg, captan caused 9/111 (8.1%), at 500 mg/kg, folpet had 3/91 (3.3%), and at 200 mg/kg, Captafol had 4/145 (2.8%). No single pesticide had a distinctive abnormality associated with it. Teratogenic defects included head abnormalities and exencephaly, short or curved tails, fused ribs, limb anomalies, and vertebral defects. The author was not able to relate these hamster data to humans [267].

(F) 2,4,5-T

Several studies have been conducted with the compound 2,4,5-T in mice to assess both the teratogenic/embryotoxic effect and the enhancement of these effects by the impurity, dioxin [268-270].

In a study by Neubert and Dillmann [268], the purest sample of 2,4,5-T available (containing less than 0.02 mg/kg dioxin) induced embryotoxic effects in NMRI mice when given orally on days 6 through 15 of gestation. The frequency of cleft palate exceeded that in controls when doses higher than 20 mg/kg (about 1/6 the LD50) were administered. While reductions in fetal weight were found with 10-15 mg/kg, there was no definite increase in embryo lethality over that seen in controls. Cleft palates were produced with a single oral dose of 300 mg/kg of 2,4,5-T; the maximal teratogenic effect was obtained when the compound was administered on day 12 or 13 of gestation. When

doses of 150-300 mg/kg were given on days 6-15 of pregnancy, 5% of the fetuses had cleft palates, as compared with about 0.7% of control animals (P=0.01). With doses of 20-30 mg/kg, no significant increase was observed [268].

In a second study, in two strains of mice (C57BL/6 and AKR), 2,4,5-T containing 30 mg dioxin/kg was teratogenic and feticidal when given orally at a dose of 113 mg/kg/day in honey or subcutaneously in dimethyl sulfoxide on days 6-14 or 9-17 of gestation. Cleft palates and cystic kidneys were seen in C57BI/6 mice, while only cleft palates occurred in AKR mice. No teratogenic effect was observed in C57BL/6 mice given lower doses (21.5 mg/kg), but cystic kidneys occurred with a dose of 46.4 mg/kg. A dose-response relationship was suggested for the feticidal and teratogenic properties of 2,4,5-T administered by either oral or subcutaneous routes [269].

In a third study, commercial samples of 2,4,5-T (containing 0.1, 0.5, 2.9, or 4.5 mg/kg of dioxin) were feticidal and teratogenic in Syrian golden hamsters when administered orally on days 6-10 of pregnancy at levels of 20, 40, 80, or 100 mg/kg; the incidence of effects increased with both the 2,4,5-T dosage and the content of dioxin. No malformations were produced by doses of less than 100 mg/kg 2,4,5-T containing no detectable dioxin. Bulging eyes (absence of eyelid) accounted for the majority of the effects caused by 2,4,5-T containing dioxin. Dioxin contamination increased the incidence of hemorrhages in liveborn hamsters and also produced marked edema [270].

(4) Reproductive Effects

The term "reproductive effects" refers to the inhibition of reproduction as distinct from teratogenesis which refers generally to the induction of malformations in the fetus. Some compounds such as DDT and Kepone, however, may exhibit both reproductive and teratogenic effects. Reproductive effects are believed to be mediated through some hormonal action of the pesticide or some effect on the endocrine system. This section discusses some pesticides, including Kepone, mirex, aldrin, DDT, dieldrin, 2,4,5-T, carbaryl, heptachlor, and crufomate, that have caused adverse reproductive effects in animals. The results are summarized in Table XIV-13.

Kepone has produced adverse reproductive effects in mice. Good et al [271] fed Kepone to mice in three experiments.

In the first experiment, Kepone at levels of 10, 17.5, 25, 30, and 37.5 ppm was fed to 66 pairs of mixed laboratory mice (7-16 pairs per treatment group including controls) from 1 month before mating until 5 months after. The average number of litters per pair decreased from 1.67 (0 ppm) to 0.2 (37.5 ppm) except for the 10 ppm group, which had 2.0. The average number of young per litter decreased from 7.93 (0 ppm) to 3.0 (30 ppm) and to 5.0 (37.5 ppm).

In the second experiment, 5 ppm Kepone was fed to 36 pairs of BALB/c mice from 1 month before mating until 4 months after. Twenty-four other pairs served as untreated controls. Treated pairs had 15.3% fewer first litters (95.8% in controls vs 80.55% in treated animals) and 28.2% fewer second litters (78.2% vs 50.0%, P=0.05).

In the third experiment, 5 ppm Kepone was fed to 20 pairs of the progeny of the treated animals in experiment two. No Kepone was fed to 23 other pairs of the progeny of the treated animals in experiment two, and no Kepone was fed to 21 pairs of the progeny of the untreated controls in experiment two. For treated animals in experiment three, Kepone was fed from 1 month before mating until 3 months after. Reproduction was decreased in treated animals and in the untreated test progeny when compared with untreated control progeny. The percent of pairs bearing first litters was 25.4%, 30.4%, and 71.4% (P=0.05), respectively. The percent of pairs bearing second litters was 15.0%, 8.7%, and 28.6%, respectively. The numbers of pups per litter were 4.40, 4.29, and 5.60, respectively, for the first litter and 5.34, 6.0, and 6.5 for the second litter. The author concluded that reproductive physiology would probably be affected by doses considerably lower than those tested in this study [271].

In another study [272], reproduction, as indicated by total offspring produced by groups of 8 pairs of mice, decreased by 23.9-87% compared with controls in BALB/cJaxGnMc mice fed 10-37.5 ppm Kepone. Average number of animals per litter, number of litters produced, and survival to weaning also decreased as Kepone concentration increased. Matings between Kepone-fed females and control males as well as between control females and Kepone-fed males at 40 ppm indicated that Kepone had an effect on the reproductive systems of both sexes, although mostly on the female [272].

Two experiments were conducted to determine the effect of mirex-induced ovulation in rats [273]. Immature Long-Evan strain rats were injected with 0.2-50 mg of mirex. After administration of pregnant mare serum (PMS), the number of ova was reduced 40-80% at all treatment levels, except at 0.2 mg, with a progressively greater effect as the insecticide dosage was increased ($P<0.05$ at 0.04 mg mirex and $P<0.01$ at 0.8-50 mg mirex). In a second study undertaken to determine whether mirex was affecting the release of luteinizing hormone (LH) or directly inhibiting follicular rupture, injections of 6, 25, and 50 mg of mirex administered 48 hours after PMS were followed by the administration of Human Chorionic Gonadotrophin (HCG). HCG overcame the inhibitory effect of the insecticide, suggesting the ovary was not the primary site of action for mirex. Injections of mirex preceding the PMS-induced release of LH inhibited ovulation, but injections following the release of LH did not effect ovulation. The data suggest mirex affects neural mechanisms which control the release of LH to inhibit PMS-induced ovulation [273].

During 1971, Deichmann and MacDonald [274] and Deichmann and associates [275], treated male and female beagle dogs orally by capsule for 14 months with either 0.15 mg/kg aldrin, 0.3 mg/kg aldrin, 12 mg/kg p,p'-DDT, or with a mixture of 0.15 mg/kg aldrin plus 6 mg/kg p,p'-DDT. Breeding occurred 0.5-9 months after dosing. Reproduction was severely affected in all four treatment groups. Out of 15 treated females, 6 had delayed estrus (with 1 or 2 of these 6 dogs in each treatment group). Two females given

DDT did not conceive after several matings. Of 11 males, 2 given 0.3 mg/kg aldrin and 1 given 12 mg/kg DDT could not mate during the study. One male given 0.3 mg/kg aldrin and one given the aldrin/DDT mixture could not mate until late in the study. All treated females had decreased mammary development and milk production associated with first litters. Regardless of treatment, half of all deliveries had stillbirths (usually one). Survival of 8 first litters until weaning was only 32% (13/32) compared with 84% of the pups of controls. All 18 control females conceived and 16 nonbreech deliveries produced 93 pups. In summary, the adverse reproductive effects from these pesticides included delayed estrus, diminished libido, presence of stillbirths, reduction in mammary development and milk production, and high offspring mortality [274,275].

Thomas [276] tested a number of pesticides for male reproductive effects in mice. Technical DDT orally administered by intubation at doses of 12.5-50 mg/kg caused a significant reduction ($P \leq 0.05$) in the prostate gland's ability to assimilate radioisotope-labeled testosterone. Labeled DDT was found to concentrate in the prostate and testes within 1-2 hours after oral administration, and amounts were still present in epididymal fat as long as 12 days later. Ten daily oral administrations of DDT at 25 or 50 mg/kg resulted in significant reductions ($P<0.05$) in testosterone accumulation in the anterior prostate. Dieldrin administered to mice similarly at 1.25-5 mg/kg for 5 days significantly reduced ($P<0.05$) uptake of labeled testosterone by the anterior prostate; 2,4,5-T likewise reduced testosterone

assimilation by the prostate at 6.25-25 mg/kg ($P \leq 0.05$) [276].

Negative results were also obtained when Thomas [276] tested parathion at 1.3-5.3 mg/kg and carbaryl at 8.5-34 mg/kg in the same manner. Neither of these inhibited testosterone uptake by the anterior prostate. Labeled carbaryl was administered once orally and amounts were found in the prostate, seminal vesicles, testes, epididymal fat, and seminal plasma. The fungicide thiophanate did not affect testosterone absorption either, although the prostate and adrenal glands showed significant increases in weight [276]. Based on the reduction of testosterone uptake by the anterior prostate, the author suggested that the OC pesticides were the principal class of pesticides that exert significant changes upon male reproductive systems.

In contrast to the previous study, Shtenberg and Rybakova [277] found that daily doses of 7, 14, or 70 mg/kg carbaryl fed to rats for up to 12 months did affect the reproductive system. After 6 months, estrous cycles were unusually prolonged ($P \leq 0.05$) by 14 mg/kg/day and likewise at 3 months by 70 mg/kg/day ($P \leq 0.002$). Sperm motility reduction, disturbed spermatogenesis, and an increase in the number of corpora lutea and atretic follicles of the ovaries were also observed [277].

Heptachlor was studied in rats by Mestitzova [278] for reproductive effects. At 6 mg/kg in the diet, litter sizes in several generations decreased and the offspring death rate increased, especially from 24 to 48 hours after birth [278].

Crufomate caused a decreased number of litters among rats

dipped once in a 10 g/liter xylene-water-emulsifier solution of the test material. The ratio of the number of litters to the number of bred females was calculated for each day of application. The only days of dipping causing significant occurrence were 2 days before and 10 days after mating [279]. Other reproduction indicators such as number of pups/litter were not significant.

These demonstrated reproductive effects in animals have taken on new importance in light of recent incidents of reduced human fertility after exposure to Kepone and DBCP as discussed in the previous section. In light of inconsistencies and insufficient evidence in studies reported above, guidelines on testing for reproductive effects are needed in order that results are consistent, repeatable, and interpretable. It is only prudent that employers and other responsible parties be aware of the possible reproductive effects cited above and take necessary precautions.

(5) Neurotoxic Effects

While acute neural intoxication by OP and carbamate pesticides through inhibition of AChE is fairly well understood, much less is known about the mechanism of the neurotoxic effects by other types of pesticides. Experimental evidence indicates that DDT and perhaps other chlorinated hydrocarbon pesticides produce neurologic effects by the inhibition of Na^+, K^+, and Mg^{2+} ATPase activity, which controls the migration of these ions at nerve endings [55]. Following is a discussion of neurological and behavioral effects observed in animals administered OC and CP

pesticides.

(A) Organochlorine Pesticides

Symptoms of acute poisoning by DDT result from effects of DDT on the CNS. DDT induced symptoms, which are generally similar in different species, begin with abnormal susceptibility to alarm stimuli, motor unrest, and increased frequency of spontaneous movements. These symptoms are followed by tremors which become constant, and as severity increases, attacks of epileptiform tonoclonic convulsions occur. DDT poisoning may ultimately result in death from ventricular fibrillation. These symptoms may be caused by a single large dose of DDT as well as by repeated exposures to the pesticide [73].

NIOSH reviewed literature on the OC pesticides DDT and aldrin/dieldrin. Several experiments discussed therein indicated that neurotoxic effects were produced by these pesticides [2,31]. Khairy [280] observed a progressive deterioration of muscular efficiency related to the amount of dieldrin administered to rats.

London and Pallade [281] found that after chronic dietary administration of aldrin to rats, at the rate of 13 mg/kg/day, 6 days/week, for 6 months and then at 4.5 mg/kg/day for 7 months, a shock-withdrawal reaction required a longer-duration electric shock to elicit the withdrawal response in treated rats than in controls. Acute dosing with a higher level of aldrin (97 mg/kg) had the reverse effect of increased excitability.

Regardless of the foregoing, the mechanism of

aldrin/dieldrin activity is not completely understood, although a metabolite may be the actual active agent [2]. The general symptoms attributed to aldrin/dieldrin poisoning include CNS stimulation, convulsions, headache, nausea, vomiting, and dizziness. Unlike DDT, convulsions may occur without previous symptoms [55].

Huber [272], as reported in 1965, fed Kepone to BALB/c strain mice and found 80 ppm or higher to be lethal to all animals in no more than 32 days. No deaths occurred when Kepone was fed at 40 ppm over 12 months. Within 4 weeks, all mice fed Kepone at 30 ppm or higher developed a constant tremor syndrome which terminated no later than 4 weeks after withdrawal of Kepone from the diet. These neurologic signs are probably correlated with the neurologic effects observed in workers poisoned by occupational exposure to Kepone [282]. Such effects included weight loss, tremor, unusual ocular motility, and arthralgia. Kepone appears to produce neurologic effects involving the central and peripheral nervous systems.

While differences exist among the symptoms caused by the OC pesticides, they do have a tendency to affect the CNS. Increased sensitivity often results and causes tremors or convulsions. These effects can be caused by high, acute dosage or by low, chronic administration.

(B) Organophosphorus Pesticides

Delayed neurotoxic effects in humans have been reported earlier for the OP pesticides leptophos and mipafox [40,87]. Axonal damage and secondary demyelination are suspected

to be the causes of such effects and result in weakness of the muscles innervated by the damaged nerve fibers. Regeneration of the nerve occurs slowly and not always completely [55].

Damage and demyelination of peripheral nerves and, in some cases, tracts in the spinal cord have been demonstrated unequivocably in experimental animals. Leptophos and mipafox, two compounds which have demonstrated similar neurotoxicity in humans, produce like effects in chickens. Chickens are the species most sensitive to these toxic effects and have been used extensively to test OP pesticides.

The neurotoxicity of OP compounds has been reviewed [283, 284]. In 1975, Johnson [283] reviewed the neurotoxicity of 226 compounds; however, most of these were not registered pesticides. Of those compounds reviewed by Johnson, haloxon [285], EPN [286,287], S,S,S-tributylphosphorotrithioate [288], S,S,S-tributylphosphorotrithioite [288], and carbophenothion [99,282] are currently registered pesticides which produced persistent ataxia when administered to chickens (see Table XIV-14). Although ataxia produced by EPN was not delayed for the usual 8-14 days [283], as is characteristic with most neurotoxic OP compounds, the ataxia was persistent and lasted more than 308 days. In addition, Gaines [99] reported persistent ataxia in chickens, lasting more than 330 days, after subcutaneous administration of EPN. Ataxia produced by S,S,S-tributylphosphorothioite, S,S,S-tributylphosphorotrithioate, and haloxon was both persistent and delayed.

In addition to EPN, Gaines [99] also found delayed ataxia

in chickens when dosed with S,S,S-tributylphosphorotrithioite, S,S,S- tributylphosphorotrithioate, and chlorpyrifos. Although delay of ataxia was 14 days for S,S,S-tributylphosphorotrithioite and S,S,S-tributylphosphorotrithioate, it was only 3 days for chlorpyrifos and was not persistent. Possible delayed ataxia caused by chlorpyrifos has not been reported elsewhere [283,284] and, consequently, further work is needed to clarify the possible neurotoxicity of this compound.

MK Johnson (written communication, May 1978) reported that carbophenothion caused delayed ataxia at 2 subcutaneous doses of 500 mg/kg. Ataxia produced by carbophenothion in Gaines' work [99] was not delayed, but was persistent, lasting more than 53 days (pericd cf observation,.

Casida et al [289] tested O-(2,4-dichlorophenyl) O-methyl(1-methylethyl)phosphoramidothioate (DMPA) by injection in hens and found that either 50 mg/kg for 10-14 days or 100 mg/kg for 7 days produced ataxia signs in 21 days. Partial recovery from the delayed neurotoxicity occurred slowly after a period of three months.

It should be noted that with few exceptions, fluoride esters of OP acids cause delayed ataxia in chickens. DFP, mipafox, dimefox, and butafox [283] are examples. Although these compounds are not registered for sale in the US, experimental or developmental use or importation of the compounds in this class could lead to undesired effects in humans. As reported earlier, two cases of delayed neurotoxicity caused by mipafox occurred in laboratory workers who were experimenting with insecticides.

(C) Behavioral Effects

Concern that pesticides may have subtle effects on human behavior, at doses lower than those which produce grossly observable neurologic effects, directed attention towards behavioral effect experiments. A number of pesticides have been tested for behavioral effects in animals. Several will be discussed here, including dichlorvos, parathion, DDT, dieldrin, and crufomate.

Behavioral effects have been observed in rat experiments with a series of chlorovinyl OP esters. Brimblecombe et al [290] found that preening activity, rearing, and defecation frequency in an open field were affected by phosphate esters at dose levels which did not cause detectable inhibition of AChE activity. The dose levels at which these effects were observed were substantially below the pesticides' LD50 values. One of the compounds tested was dichlorvos (DDVP). The minimal effective single dose of DDVP required to produce the behavioral changes observed was approximately 0.2 mg/kg. The ratio of the LD50 of DDVP to the effective behavioral dose was 175. Other compounds tested were 2-chloroethyl-2,2-dichlorovinylethylphosphonate, 2-fluoroethyl-2,2-dichlorovinyl methylphosphonate, and 5 similar synthesized esters. The ratio of LD50 to effective behavioral dose for these compounds ranged from <3 to >100.

In another study, Reiter et al [291] studied parathion's effect on learning in mice. Subchronic oral doses consisting of 1-4 mg/kg parathion on 6 successive days prior to a learning trial did not affect learning, despite observed depression of

blood AChE activity. The authors suggested that compensatory mechanisms were operating which allowed the mice to learn even after repeated parathion administration. However, in a separate experiment a single acute dose of 6 mg/kg parathion after an 18-hour fasting period (approximately one-third of the LD50) abolished learning capabilities in the 90% surviving mice.

Despite the apparent effects of acute and chronic exposure to OC insecticides upon the CNS, until recently, little attention had been paid to the influence of these compounds on behavioral systems. Scudder and Richardson [292] found that DDT in very low doses (0.1 or 1.0 mg/l) in drinking water of pregnant mice and their offspring resulted in a significant decrease in the aggressivity of isolated young males. Sobotka [293] reported alterations in several behavioral and neurophysiologic parameters in mice after single low doses of DDT. Exploratory activity in an open field was significantly enhanced 24 hours after a single oral dose of 25 mg/kg of DDT. At the same time, the ability of animals to habituate to the open-field situation was reduced. In a passive avoidance test, DDT in doses lower than 25 mg/kg alleviated stress-induced motor depression. Changes in the maximum electroshock seizure patterns reflected an increase in brain excitability. It has been suggested that DDT may facilitate the central excitatory process, at least partially, by a disinhibitory mechanism.

Peterle and Peterle [294] studied the effects of feeding 7 ppm technical DDT on the aggressive behavior of male mice. Mice given DDT "lost" more bouts (as determined by posturing and

avoidance behavior) and made fewer biting attacks than controls. The DDT-fed mice were significantly less aggressive than control mice and were more likely to submit in territorial fights.

Smith et al [295] exposed 7 squirrel monkeys to dieldrin at two oral doses of 0.10 and 0.01 mg/kg/day for 55 days. Two zero-dose controls were included. All 9 monkeys were taught a visual nonspatial successive discrimination task. Ability to learn this task was severely retarded in the high-dose group ($P<0.003$) but not in the low-dose group, when compared with controls.

At the end of 55 days, the higher dose group was shifted to the low dose, the low-dose group was shifted to the high-dose, and the controls continued at zero exposure. During the following 54 days, all group performances remained at approximately the levels achieved at the end of the preshift period. The authors concluded that the high dose had disrupted learning acquisition, and speculated that this effect was due to disruption of the activity of the hippocampus, which is necessary for initial learning but not for retention of a learned task. This appears to demonstrate state-dependent learning.

Results of the animal behavioral studies cited above are in some cases inconsistent and are often too scant to serve as a basis for recommended control procedures. However, they do point out the possible subtle changes that may take place in humans exposed to various pesticides.

In summary, many factors, including individual susceptibility due to variations in genetic makeup of

individuals, age, sex, synergism caused by multiple exposures, fractionization of doses, and extrinsic factors such as temperature, affect the toxicity of pesticides. Attention should be given to the chronic irreversible effects demonstrated for certain pesticides. Carcinogenic and neurotoxic effects of certain pesticides have been demonstrated in man and animals, and the literature reveals a substantial number of reports on teratogenic and mutagenic effects in laboratory animals and in in vitro test systems. A continuing controversy is the use of animal toxicologic data to predict effects in man, but it is well established that many toxic effects observed in humans were observed first in experimental animals. Accordingly, the use of animal data as a surrogate for human data is warranted in order to anticipate potential human toxic effects and to develop the best and safest protective mechanisms in the manufacture and formulation of pesticides.

IV. ENGINEERING CONTROLS

Worker exposure to pesticides can occur during manufacturing and formulation when chemicals spill, leak, or discharge from the process system and contaminate areas where workers are present. The most frequently reported industrial exposure occurs during the transfer of materials [29]. Product packaging, drum and barrel filling, and bag or sack filling are typical transfer operations with high exposure risks. The entry of workers into systems, equipment, or enclosures that are contaminated may occur inadvertently, but routine servicing, nonscheduled maintenance, and process monitoring appear to be the kind of activities with potential for significant exposure. [29].

Both types of exposure can be controlled and reduced by the proper design, construction, use, and maintenance of plant equipment. Engineering controls are less influenced by unpredictable human factors than are work practices. They are usually more reliable and effective, and when coupled with a well-designed preventive maintenance program, constitute the preferred control strategy. However, due to the wide variety of processes and equipment used in the pesticide industry, detailed engineering specifications must vary with the situation in a specific facility. Differences between processes exist in the operating pressures and temperatures, in the toxicity of the

materials handled, in the physical properties of the materials, and in the climatic conditions, all of which affect the design of engineering controls.

Current workplace air standards (29 CFR 1910 Subpart Z) and previous NIOSH criteria documents dealing with pesticides (Appendices III and IV) have circumvented the problems associated with specific facility situations by establishing environmental (workplace air) exposure limits which dictate a performance standard but leave actual design of controls to employers. Engineering controls should prevent exposures greater than those specified.

The general principles of control strategy and engineering controls for pesticides are best illustrated by reviewing past instances of exposure and observations made during recent plant visits. Exposure caused through pesticide escape from equipment intc work areas can be by avoided by enclosing and isolating process systems. In those cases where exposure occurs when workers enter contaminated process areas, application of remote handling techniques to sampling and equipment servicing operations will provide protection. Engineering controls are applicable in existing operations through retrofitting. In new plants, appropriate controls should be incorporated in the original designs.

In the following sections, the basic processes involved in pesticide manufacture and formulation are described. Some cases of worker exposure and pesticide escape are cited and discussed and suggestions for appropriate engineering controls are made.

Following this process overview is a review of specific problems common to both pesticide manufacturing and formulating operations, including materials transfer, packaging, leakage, intentional or unintentional discharges, equipment maintenance, and process monitoring. The equipment and areas where failure or employee exposure are likely to occur are identified. Engineering controls that can be implemented to control these exposures are described.

Manufacturing Processes

The methods and processes used in pesticide manufacture vary as greatly as the chemical structures of the products. Manufacturing can be accomplished on a continuous basis, on a batch basis, or on a semicontinuous basis. Despite the variety of processes, most pesticide manufacturing can be broken down into the same basic process steps.

First, raw materials are made available for processing. Some starting materials are delivered and stored at the plant. However, because many pesticide operations are part of a larger integrated chemical plant, raw materials are often produced on site. For example, chlorine, an ingredient in the manufacture of many pesticides [296], is produced by some companies for use in their pesticide synthesis [8(p 24)]. Raw material storage and dispensing operations have their own health hazards. For instance, the human carcinogen vinyl chloride is a raw material used in making endrin [8(p 32)]. Maddy and Edmiston [297] reported an exposure to hexachlorocyclopentadiene, another

ingredient in pesticide manufacturing, in the transfer of raw materials. The following are examples of intermediates used in the production of pesticides: arsenic trioxide, acrolein, ammonia, aniline, atrazine, benzene, bromine, bromochloromethane, butyl mercaptan, carbon disulfide, cresol, dioxane, diphenylamine, epichlorohydrin, ethylene dibromide, ethylene oxide, formaldehyde, hydrogen sulfide, methyl chloride, phenol, phosgene, sodium hydroxide, sulfuric acid, thionyl chloride, and trichloroethylene [298]. Some of these chemicals are also registered pesticides.

The next basic part of pesticide manufacturing is actual production of the pesticide chemical. In the processing of natural pesticides, such as pyrethrum, refining is the only step. Otherwise, production begins with synthesis of the pesticide in a single or multistep chemical process. Virtually every basic type of organic chemical reaction is involved in the manufacture of pesticides [298]. Monitoring the chemical reaction as it takes place allows an optimization of the pesticide synthesis, but exposures have occurred from opening sample ports [128] and from analyzing samples [297].

Synthesis is usually performed in reactors which may be equipped with coils for temperature control and with an impeller for mixing. Maintenance of such pesticide reactor equipment has resulted in serious worker exposures [113].

The next step in the manufacturing process is the separation of the pesticide from unreacted ingredients, such as sulfuric acid in DDT manufacturing, from by-products, such as

sodium sulfate in DDT manufacturing [296], and from solvents, such as dioxane in monuron manufacturing [298]. Separation is performed using various equipment, such as filters, extractors, strippers, and centrifuges. Centrifuging has been a potential emission source in the manufacturing of aryloxyalkanoic acids [299]. Some residual pesticide will be present in the separated materials; therefore, containment and treatment may be necessary before disposal or reuse. Brown [143] reported eye and skin injury from exposure in a manufacturing plant where unused reactants were recycled to synthesize triazapentadienes.

Pesticidal chemicals are usually further refined in another purification step. In some cases, impurities in pesticides may pose a greater health hazard than the pesticide itself. A number of cases of toxic reaction to tetrachlorodibenzodioxin (TCDD) contamination in chlorinated phenol-derived pesticides have been reported [53,124]. The equipment commonly used to purify pesticides includes extractors, stills, evaporators, and dryers. When ventilating air passing through that equipment is used to transport contaminants, it may also carry pesticides. Such operations require controls to prevent worker exposure.

The final major step in pesticide manufacture is that of packaging. Depending on customer requirements, pesticides may be packaged in a variety of vessels ranging from small glass containers to railroad cars. The packaging system used is a function of product form, ie, powder, dust, liquid, granular solid, or gas. The packaging operation may be performed remotely with automatic dispensing, weighing, and sealing equipment but is

more frequently performed with a local exhaust system or without any specific controls. A packaging operation in which there is no attempt to limit the entrance of pesticide vapors, gases, dusts, or aerosols into the atmosphere of the workplace has a large potential for worker exposure [8].

Formulating Processes

While manufacturing is a chemical process yielding technical grade pesticidal chemicals, formulation is a physical process yielding a finished pesticide product with the form and strength required for its specific use. There are over 40,000 Federally registered pesticide formulations, but the physical form of each is limited to a few basic categories as discussed below [1].

(a) Dusts

Dusts are formulated for use without additional processing. The active ingredient or pesticide is diluted to a concentration usually ranging from 0.1 to 20.0% by mixing with a diluent or carrier [300]. Ingredients commonly used as carriers in dusts include flour, lime, gypsum, sulfur, sand, clay, and talc. Although these ingredients are described as inert with respect to pesticide strength, several are recognized health hazards: Talcs sometimes contain asbestos fibers, and certain allotropes of sulfur are effective pesticides in themselves. Other additives include stabilizers and dyes.

As are most formulation operations, formulation of dusts is a batch process. An example is the formulation of mercurous

chloride into its final form. First, the mercurous chloride is emptied from its container into a mill. After grinding, it is transferred to a mixer for blending with fine clay and a vegetable dye to add color. Mills used for grinding dusts include hammer mills, impact mills, vertical roller mills, and fluid energy mills. The blending of solids is performed in a rotary drum mixer. The final product is packaged in 10-gallon fiber drums [296].

Hartwell and Hayes [301] compared the health effects of worker exposure during formulation of parathion and mevinphos dusts and measured the frequency of poisoning cases and inhibition of cholinesterase (ChE) activity. The study indicated that concentrations of airborne dust were frequently high enough to produce severe symptoms in exposed workers. Engineering controls that would prevent such exposures include local exhaust systems operated together with an effective general ventilation system and a clean, filtered air supply. With proper attention to the design of such systems, one can readily control airborne dust.

(b) Wettable Powders

Powders may be formulated for dispersion in water before use. Wettable powders can be made with the same equipment as dusts. These powders usually contain 15-75% active ingredient, 1-2% surfactants, and the balance is made up of inerts [300]. For instance, DDT has been blended with silica, a wetting agent, and a dispersing agent, to yield a 76% DDT wettable power. Subsequently, the mixture is ground to the desired particle size

and packaged in 50-pound bags [296].

Wolfe and Armstrong [18] conducted a survey of potential worker exposures in the formulation of 50% DDT wettable powder. They found that the worker who dispensed ingredients into the blender had a potential exposure of 33 mg DDT/hour. The bagger who filled 50-pound bags had a potential exposure of 160 mg/hour, while the bagger of 4- and 5-pound bags had a potential exposure of 539 mg/hour. These differences in exposure levels are directly related to the number of containers handled by the bagger, to the number of container opening and closing operations, and to the number of filling operations, all of which have exposure potential. Wettable powders can be controlled with systems of similar design to those required for dusts.

(c) Granules

Granular formulations are intended for direct aerial and ground application. Their compositions are similar to those of dusts, but the method of preparation is different. A granular carrier within a 30-60 mesh particle size, such as vermiculite, diatomaceous earth, ground corn cobs, or bentonite is impregnated with a solution of the active ingredient. Insoluble solid pesticides are melted for impregnation. The actual process involves spraying the carrier with active ingredients while the material is mixed in a ribbon or drum blender [300].

Deeken [134] reported six cases of chloracne arising from exposure to 2,6-dichlorobenzonitrile, the active ingredient used in a granular formulation. Contamination of workers' skin and clothing can be controlled by complete enclosure of the operation

within a ducting system and remote operation or monitoring of the spraying operation. A secondary measure of protection would be provided by a well-designed local exhaust system to assure continuous removal of airborne particulates or mists.

(d) Emulsifiable Concentrates

Emulsifiable concentrates represent the liquid phase equivalent of wettable powders. The concentration of active ingredient usually ranges from 15-80%; surfactants constitute about 5%; and the balance is an organic solvent such as xylene, methyl isobutyl ketone (MIBK), or amyl acetate [300]. The ingredients are blended in an impeller-agitated mixing tank. For example, disulfoton, an OP, is dissolved in xylene, and packaged in 1-, 30-, and 55-gallon drums [296].

(e) Liquid Formulations

Liquid formulations are ready-made for application by spray or dip. Pesticide solutions are often formulated by dissolving active ingredients in the appropriate solvent. The solution is agitated in a mix tank, often equipped with cooling coils which maintain a desired reaction temperature. Before being pumped into containers, the solution may be filtered. Examples of such formulations are trifluralin, 4 pounds/gallon, in aromatic naptha (mineral spirits), and 20% pyrethrin in deodorized kerosene [296]. Such formulations may be packaged in metal containers ranging from a 1-quart to 55-gallon capacity.

Maddy and Edmiston [297] reported three cases of mevinphos poisoning among formulators handling liquid pesticides in open systems. The most frequent cause of exposure was from

malfunctions in the mixing tanks or from worker entry into these tanks. By their nature, liquid formulations and emulsifiable concentrates are more easily controlled than dusts and are more amenable to enclosure and isolation.

(f) Aerosols and Fumigants

An aerosol is characterized by its form of packaging and by the suspension of fine solid or liquid particles that result in its application. These pesticides are held under pressure in cans or bottles and are applied directly from their containers by spraying. Aerosols usually consist of 2% or less of the active ingredient, and the remaining ingredients consist of a solvent, a propellant such as nitrogen or carbon dioxide, and any of a wide range of additives. Because such formulations are widely used in homes, they may contain odor suppressants, perfumes, antimildews, repellents, or synergists such as piperonyl sulfoxide, propylisome, or piperonyl butoxide. The purpose of the synergist is to promote the action of the pesticide [296].

Fumigant formulations are generally self propelled; the active ingredient concentration is usually 90% or more and the propellant is 10% or less. Methyl bromide is stored in closed refrigerated systems and packaged in gas cylinders, together with chloropicrin whose lacrimating effect serves as a warning agent [296].

Maddy and Edmiston [297] cited the case of a pesticide formulation worker who was burned by methyl bromide when it escaped from a closed distribution system. The filling and handling of pressurized containers carry a risk of explosion or

other release of material. California recorded an instance of eye injury when an exploding can of insecticide caused chemical conjunctivitis [297]. In processes used to prevent condensation and corrosion within the container, many gases are dried over silica gel before packaging, leaving contaminated silica gel that must eventually be removed and replaced.

Problems in pressurized systems frequently arise from leaks at jcints, connections, on-off valves, and pressure relief valves. In some cases, corrosion within the system is a result of chemical interaction with lubricants and sealers. Engineering controls that can be applied include remote handling and monitoring, pressure sensors, and frequent maintenance to detect corroded or loose fittings before failure occurs.

Equipment and Process Controls

Certain basic types of equipment and processes are used in both the manufacture and formulation of pesticides. The equipment is subject to failures and other problems resulting in worker exposure. The following sections discuss some of the particular equipment involved, particular modes of failure, and the common problems associated with pesticide operations. Specific cases of reported worker exposures to pesticides are cited and discussed as well as the engineering methods that should be used to prevent such exposures.

(a) Materials Transfer

The specific hardware associated with materials transfer includes piping systems, pumps, valves, couplings, belt conveyors

and bucket elevators, hoppers and receiving bins, and holding and dispensing tanks. Pipes, hoses, and lines are potential sources of pesticide emissions since they may rupture and leak at joints. Pipe rupture can result from improper materials usage, excessive pressures, excessive temperatures, vibration or chafing, and corrosion or clogging. All piping should be constructed of the appropriate material necessary to withstand the anticipated pressures, temperatures, vibration, and corrosion. Pipe runs should be mounted in a position to avoid accidental impacts.

A case in which a pressure hose burst and sprayed two employees who were using the hose to fill a drum was reported in 1975 [29]. The author stated that even though the employees were wearing safety equipment, they both experienced undesirable health effects as a result of the exposure. This problem was subsequently solved in this case through replacement of the flexible hose by a metal pipe. If a flexible hose is absolutely necessary, then it should be replaced periodically as part of a basic preventive maintenance program.

Pesticide emissions can occur at pipe joints that are flanged and bolted. Even if the system is originally tested and found to be tight, normal vibration and deterioration of gaskets and "O" rings will eventually cause leaks. Wherever feasible, welding of pipe joints can be used to avoid these problems.

Exposures frequently occur when piping systems are opened to remove obstructions. An employee was exposed to dibromochloropropane while attempting to unplug a line [26]. While further details of this case were not available, such

exposure can usually be prevented by isolating the line in question and by flushing it with a solvent rather than by opening the system.

Auxiliary piping systems that are not actually conveying pesticides also have the potential to cause pesticide exposure. In a case in California [29], a hot water line ruptured and sprayed an employee and a conveyor belt carrying diazinon powder. The powder, in turn, splashed on the employee, and he later substained first degree chemical and thermal burns. This incident demonstrates that proper design, material selection, location, and maintenance of piping systems are important in preventing worker exposures.

Pumps present many of the same exposure problems as do piping systems. Joints and seals, materials selection, cleaning, and batch changes are common problems. Pumps also reguire preventive maintenance if unscheduled shutdowns are to be avoided. Part of this maintenance program should include a thorough check of all moving parts, and particularly a check of the pump seals for signs of leakage. Two cases were reported [29,297] of worker exposure to pesticides during a pump repair operation and indicate that pumps be cleaned to reduce the possibility of exposure before they are worked on. This is done by purging the pump with a solvent and washing down the pump exterior.

Langner [302] suggested that pumps handling cancer suspect agents should be provided with vacuum lines and shrouds around the seals to remove any substances that might leak during

operation. When the materials handled are not highly toxic or volatile, the pump can be mounted on a grating over a collecting sump or can be surrounded with a dike or curb. In these cases, separate arrangements are necessary to clean up and remove spilled material. Cleanup often can be handled using sorbents, diluents, or a local exhaust system attached to the pump.

Leaks at couplings can cause worker exposures to pesticides during connecting and disconnecting operations. At least two cases of workers being heavily exposed to pesticides while in the process of coupling or uncoupling a line have been reported [29,297]. Exposures of this type may be prevented through the use of a dripless connector. Conveyors and bucket elevators have a potential for serious exposure problems since they frequently are not operated in enclosed systems. Pesticides can escape at feed, transfer, and dump points. Therefore, belt conveyors and bucket elevators should be enclosed in a duct, which is connected to an efficient local exhaust system.

Enclosed conveyors and elevators must be entered by maintenance personnel to clear jams, to lubricate moving parts, to replace and repair components, and to adjust belts and rollers. The enclosed system must, therefore, contain suitable hatches for performance of maintenance and also for removal of accumulations of dirt and solids.

Hoppers and bins are generally open-topped and may represent another serious exposure problem. During filling, the air displaced by the incoming material is usually laden with dust, and dust is also produced during emptying. These

containers have to be entered when they become clogged and when their levels need to be manually checked.

Dust emissions from bins and hoppers can be controlled through the installation of local exhaust systems and with the provision of lids for use when filling. Dumping can be performed remotely and the dust removed by local exhausts. Problems of caking, bridging, and rat-holing in hoppers can be solved through the use of low-pressure pneumatic blasting devices built into the hopper walls and operated remotely to improve material flow and to eliminate the need for workers to free the material by poking and prodding.

Holding tanks are generally close-topped liquid containers. Workers at storage tanks may be exposed to pesticides in air displaced by venting or filling, or by leakage from seams and connections. The air escaping from tanks can also cause undesirable health effects. Spillage from tank caps can occur when tanks are overfilled accidently, or when high temperatures result in expansion of the tank contents. Pressure relief valves can release pesticide-laden air. Tanks must often be entered for cleaning or replacement of the lining. Checking liquid levels in tanks is often performed by opening a port and using a dipstick.

Several engineering controls including remote liquid level sensors, ventilation lines for pressure relief valves, and concrete dikes to contain spills; temperature and pressure sensors can be added to reduce pesticide emissions. Level sensors can be arranged to operate automatic shut-off valves at any desired liquid level. Systems can be fitted with

pressure-sensing devices, so that when the integrity of enclcsures or seals is lost, pumps may be automatically shut off [8(p 56)].

(b) Packaging

Packaging is a special case of materials transfer but deserves individual attention since it is in the packaging operation that significant opportunities for exposures occur. The chance for exposure increases because the system is usually open at this point.

Pesticides can be packaged in a variety of forms including powder, liquid, dust, granules, or pressurized aerosol. The material is contained in a hopper or tank and is dispensed into the package by weight or volume. In manual packaging operations, the containers are placed and removed at the packaging station and transferred to the sealing station by employees. Considerable potential exists for worker exposure due to displaced air, dust, overflows, spillage, improper sealing during filling, lack of or poor ventilation, failure of bags, rupture of delivery hoses and lines, and a variety of other causes. While automatic systems can suffer from similar failures, the operation can be entirely enclosed and can be remotely operated and contrclled to prevent worker exposure.

Packaging equipment subject to failure includes the entire piping and mechanical system of the filling machinery, delivery hoses, conveyor belts, weight or volume sensors, lifting and transfer mechanisms, and the containers themselves. The containers can vary from small glass bottles to fiber drums and

bags to 55-gallon drums and railroad tank cars.

Comer et al [12] conducted tests for body front exposure in three formulating plants during formulation of 4 and 5% carbaryl dusts. The workers studied were at bagging or mixing stations, generally areas of greatest potential contamination. One of the factors observed as causing occasional high exposure values was malfunctioning of the bag filler spout mechanism, resulting in excess billowing dust. The formulating plant workers' mean respiratory potential exposure as determined by contamination of respirator filter pads was 1.1 mg/hour of work activity. To compare values, the authors also conducted tests on spraymen operating tractor-drawn airblast equipment as they applied 0.045% carbaryl spray in fruit orchards. For spraymen, the mean potential exposure value was 0.09 mg/hour. While the above report does not provide any additional details, it is likely that the bagging operation was not protected by an efficient local exhaust and hood system which could have materially reduced the fugitive carbaryl dust noticed in the study.

Open transfers are encountered where repeated emptying or filling of small containers makes permanent conduits for transfer impractical. Airborne exposures were reported [299] in the open packaging of DDVP into aerosol cans. Following filling, the cans travelled down a conveyor line to the capping station. The distance was apparently long enough so that evaporation from the cans could be the only apparent cause of the illness.

At least four cases of employees being splashed with pesticide during liquid packaging operations were reported in

California in 1975 [29]. In the first case, methomyl was splashed on an employee while he was filling containers. If a closed and automatic packaging system had been used, this exposure would not have happened. In the second case, a worker was filling and capping drums of mevinphos when some of the chemical splashed on his arm. Again, a remotely controlled automatic packaging system could have prevented the exposure. In the third case, a broken nozzle sprayed an employee on the face, chest, and legs. Suitable enclosures or a remote control system could have also prevented this exposure case. In the fourth case, an employee was splashed in the eyes with sodium pentachlorophenol while filling 50-gallon drums. To minimize splashing, employees could "bottom fill" drums, not "top fill" them [8(p 27)], and should wear eye protection. More effective protection would be provided by remote-controlled filling operations.

Flexible or quick disconnect attachments could solve these problems encountered in pesticide packaging operations. An example is shown in Figure XIV-1. Plastic bags secured with shock cords were used by one manufacturer/formulator where rigid connections were not appropriate [8(p 97)]. A flexible bellows duct can also be used as a rapid connect/disconnect system as seen in Figure XIV-2.

Air displacement is another source of pesticide emissions during packaging. As air leaves a container being filled, its countercurrent flow tends to entrain materials and carry them into the surrounding area. Such an emission can lead to worker

exposures, as reported in the bagging of propargite [29]. During packaging of liquid, a vapor return line from the receiver to the dispenser can control potential emissions. Such a device has wide application in the petroleum industry [8(p 81)].

A local exhaust ventilation system can collect dust-laden air displaced during solids packaging operations (Figures XIV-2 and XIV-3). This type of ventilation system only protects workers when it is properly designed and installed. Airflow must have sufficient velocity to entrain the airborne contaminants and to be directed away from the worker, past the pesticide material to the hood, thus ensuring that contaminants do not pass through the workers' breathing zone. Maddy and Edmiston [297] pointed out the importance of hood location in protecting a fungicide bagger by ventilation.

Exhaust ventilation systems may be used in conjunction with other systems. The exhaust ventilation in the packaging operation in one plant has been complemented with a vacuum system for collecting spilled or leaked materials [8(p 57)]. In addition, a fresh-air duct and plenum system provides make-up air without crosscurrents to interfere with exhausting hoods. Although complete enclosure of packaging operations may be difficult because of the requirement for frequent changes of containers, the three systems together are effective in controlling personal exposure.

Examples of worker exposure discussed above illustrate the need and the methods for eliminating exposure during pesticide packaging operations. The occasional gross overexposure or

repeated low level exposure to a toxic chemical certainly warrants the implementation of positive packaging controls.

(c) Equipment Leakage

Most items of equipment used in formulating or manufacturing plants may develop leaks. A comprehensive preventive maintenance program is a necessity if leaks are to be detected, prevented, and controlled. In addition to piping systems and pumps that have been discussed previously, leaks can be anticipated in reactors, filters, separators (including solvent strippers, extractors, condensors, and scrubbers), dryers, doors, and inspection ports.

Locations where pesticide emissions from reactors can occur include vents, charging doors, sampling ports, and agitator seals. Releases can also occur if pressure buildup is sufficient to operate the pressure relief valves when a reactor is manually loaded, or when a dipper is used to obtain samples of the reaction mixture during processing. Reactor vessels should be maintained at pressure negative to the atmosphere so that all leaks are inward.

Releases during charging and venting can be controlled through the installation of local exhaust systems. Exposures during sampling can be eliminated through the installation of valves that do not permit workers to be exposed to pesticides when obtaining samples. Agitator seals can leak due to loss of flexibility and normal deterioration, or as the result of drive shaft eccentricity. This type of leakage can only be controlled by inspection and replacement of worn seals.

Davay [128] reported a case of fatal kidney damage in a worker exposed to methyl bromide during its manufacture. The worker was exposed during a shift when the reflux reaction of methanol with liquid bromide was proceeding in the reaction vessel. He worked for 3 hours within a radius of about 12 feet from the sampling and filling valves near the receiving vessels. Findings revealed that methyl bromide apparently escaped from an open sampling valve which the worker noticed and closed. Death occurred 18 days later as a result of severe injury to the central nervous system and kidneys. This accident could probably have been prevented if the sampling valve had been connected to a buzzer, indicator, or warning flag when it was opened.

Filters are used to separate solids from liquids or gases. Leakage is generally due to deterioration of seals, gaskets, and filter frames, allowing the pressure release of pesticidal chemicals. Additional exposure can result when the filters are replaced or cleaned. Leaks can be spotted and exposure controlled through regular inspection and maintenance.

Leaks from separators occur when pressure buildup causes pressure relief valves to operate and to release air containing high concentrations of pesticides. Engineering controls that are applicable to prevent releases from scrubbers and separators include local exhaust systems to remove vented contaminants from pressure relief valves and pressure sensors that can give advance warning of excessive pressure buildup.

Dryers are used in pesticide manufacture to remove solvents from slurries and to obtain a powdered pesticide product.

Pesticide emissions from dryers can occur when the airstream is ducted to an exhaust system, whenever there is a mechanical or materials failure, and when the powdered pesticide is removed or dispensed. Stationary local exhaust ventilation dedicated to one system can reduce or eliminate these emissions. However, it is important to ensure that the entire ducting system is operated at a pressure lower than ambient atmospheric pressure and that fans and ducting are properly sized and free of severe bends or obstructions which might restrict airflow.

When the dried pesticide chemical is dumped from the dryer, workers may be exposed to the dust. A blender-dryer in an endrin manufacturing plant developed a problem of this nature [299]. The pesticide was dispensed through a gate valve at the base of the blender-dryer. The valve was operated by an employee allowing the pesticide to enter the packaging hopper. When operating the valve, the employee was in the direct path of the dust rising from the hopper with considerable exposure potential. The dispensing system should be operated remotely through an electrically controlled valve, and the discharge chute should make a direct connection to the hopper.

Leaks can also occur when doors or inspection ports are left open or are not properly closed. All doors and ports should be equipped with a self-closing mechanism, or with a device that will provide a warning or system shutoff until the door or port is fully closed and latched.

The escape of materials through ducting can be minimized or eliminated by maintaining the duct interior pressure at a

pressure less than ambient atmospheric. This same principle is applied in ventilation ducting where fans are located at the downstream end of the system to ensure that any leaks in the ductwork are into the duct and not from the duct to the outside environment.

When leaks occur, it is essential that they be detected and controlled immediately. Equipment for leak detection may include line sensors to measure pressure and flow, or chemical sensors to detect the presence of a substance outside the system. Many such leak detection systems can be integrated into a general warning and alarm system and can also act to operate shutoff valves or to shut down entire systems. Visual detection of leaks can be aided by adding a dye to pesticides. Odorous chemicals may be added to liquids or gases to serve as a leak detection device. For physical inspection, suspected leak areas can be painted with soap solution or a similar indicator.

Certain operations may be amenable to complete containment in separate buildings or in closed rooms, thus providing a "secondary containment" of spilled liquids or dust. All operations can be controlled and monitored remotely, and in the event of a leak, the entire room can be purged or flushed before maintenance workers are permitted to enter. Operational areas should be in buildings well removed from personnel service buildings such as locker rooms, showers, cafeterias, and offices.

For certain leaks, temporary control may be effected through the utilization of local exhaust systems with flexible hoses and portable hoods, or with a vacuum system to clean up

spills. Leaking gases and vapors, or liquids with high vapor pressures may diffuse too rapidly to be contained by such temporary measures, and forced air purging of the entire area may be required.

An exposure recorded in California [297] led to the application of forced air ventilation in a formulating operation. The employee involved had removed his safety equipment while working near a holding tank containing mevinphos. A forced air ventilation system was subsequently installed to remove emission concentrations in the holding tank area.

(d) Equipment Maintenance

The maintenance of chemical processing equipment in the manufacture and formulation of pesticides requires a variety of cleaning and maintenance tasks that may expose workers as they use equipment. During 1975, California reported that equipment maintenance operations ranked second to material transfer operations in causing pesticide exposures in the pesticide formulation industry [29].

Two cases were reported in which workers were exposed to pesticides while repairing pumps [29,297]. In both cases, residual pesticides were responsible for the exposure. The investigators suggested that pumps should be cleaned in a "remote mechanical manner" before maintenance is attempted, suggesting that pumps should be purged, disconnected, and thoroughly washed down with solvents or water prior to maintenance work.

Components of many items of equipment require periodic inspection and replacement. Examples are filters, gaskets,

packings, linings, refractory materials, shaft seals, and so on. A recent report [299] on heptachlor manufacture noted the exposure hazard inherent in the servicing of a process filter. Unclogging blocked transfer lines or cleaning out tanks may require that closed systems be opened or that workers actually enter pesticide-contaminated equipment. An exposure to DBCP in California reportedly occurred when an employee attempted to clear a plugged line [29].

The variety of products produced by batch processing in many formulating plants calls for frequent isolating, purging, cleaning, and reconnecting of equipment. Systems with a need for frequent maintenance or cleaning should be installed in duplicate to permit a given unit to be withdrawn from service and to allow a process to continue without exposing maintenance personnel. Special attention must be paid to the design and testing of connections that must be frequently broken and reconnected for equipment maintenance or cleaning purposes.

Closed equipment cleaning and blockage cleaning can be facilitated if water, compressed air, and steam supply connections are permanently installed on or in equipment. Similarly, purging can also be facilitated if appropriate connections are available.

Grinders and mills require periodic cleaning and replacement of the rollers or balls. To perform these operations, it is often necessary for maintenance staff to enter the equipment. Before this is allowed to occur, the grinder or mill should be thoroughly cleaned with solvents and steam and

tested to ensure that the equipment is effectively decontaminated.

Weight hoppers can present a servicing hazard to persons not employed by the using facility, since the weighing mechanism is usually serviced by an outside company whose employees might not be as conscious of pesticide hazards as the regular plant employees. Steam cleaning of weight hoppers and scales is recommended before maintenance work is permitted.

Mixers and blenders have to be cleaned periodically and their moving parts serviced and lubricated. Again, thorough cleaning with solvents and steam is necessary before workers are permitted to enter.

Vibrating screens and filtering systems must be opened periodically for screen or filter replacement or for the removal of oversize particles. Screens and filter systems frequently contain heavy concentrations of dust which can produce respiratory, eye, and skin exposures if the dust is not removed before the system is opened. Similar conditions are encountered in the maintenance of belt conveyors and bucket elevators.

(e) Process Monitoring

Monitoring the various processes encountered in the manufacture and formulation of pesticides may require visual observation, measurement of physical parameters, or collection of chemical samples. If these operations are conducted through an open port or access door, the worker involved may be exposed to pesticides.

A recent report indicated the potential for worker exposure

during sampling [299]. In some cases, samples were taken by opening a valve and allowing the sample to run into a container, while at other times, samples were taken by lowering a dipper into the chemicals through an inspection port. The latter process can result in severe exposures. Pressure can build up in a reaction vessel, so that subsequent opening of the sample port can splash pesticides around and beyond the opening. When using the sample dipper, the employee could potentially come into contact with the rim of the sampling port, or could insert the dipper too far into the mixture and immerse his hand. Another problem with sample ports is that employees frequently leave them open, which permits continual exposure of all workers in the vicinity.

Sampling systems that require the use of hand-operated dippers should be eliminated in favor of those that are controlled by a valve. Sampling done indirectly through closed-loop sampling systems can prevent exposures [8(p 80)].

Many operations in process monitoring can and should be performed remotely. Direct observations of physical or chemical processes can be made through view ports or through the use of remote television monitors and receivers. If a large number of sensors are used to monitor operation of equipment, readouts can be displayed on a central control panel which can also serve alarm and security functions.

(f) Environmental Discharges

While the discharge of pesticidal chemicals from industrial plants is certainly an environmental concern, it is also another

cause of worker exposure. Ventilation system exhausts, process air from drying operations, and vapors from pressure relief valves can release pesticides into the air. Overloaded systems can also contribute to this problem. A case was reported [29] of a worker in a plant manufacturing sulfuryl fluoride gas who suffered effects from the gas released by an overloaded scrubber. The company owning this plant planned to install a larger scrubber system capable of handling the fumes.

Plant runoff, drainage, and process waste water may leave pesticides deposited in or near working areas. These releases can eventually result in undesirable accumulations and resultant exposure hazards. Materials may also be drawn back into the plant through recirculation from exhaust stacks into fresh air intakes caused by poor design, location, or unfavorable winds. All gases and liquids exhausted from the plant or otherwise disposed of should be freed of their pesticide content before release.

Discharge air may be cleaned by physical treatment in cyclone separators, scrubbers, baghouses, or electrostatic precipitators, or may be treated chemically by flaring, catalytic afterburners, or absorption towers [303]. Discharge water may be purified before release by filtration, settling, or by chemical treatment [304]. It is emphasized that chemical decontamination and neutralization are preferred cleaning methods. The mere separation of pesticides from discharge streams adds to the problem of disposing of recovered materials. For example, periodic emptying of a dust collector requires that provisions be

made to prevent dust from again becoming airborne [297]. Application of wet methods may be useful in these instances.

V. WORK PRACTICES

Ideally, pesticides should be manufactured and formulated within enclosed, remotely operated systems to isolate them from workers. However, even with such systems, opportunities for exposure arise. Workers must be protected while the systems are being installed and tested. Systems may break down, causing leaks and demanding the attention of maintenance workers. Periodic cleaning of process equipment and sampling may also call for the opening of closed systems. Fires, floods, and other calamities may cause the breach or destruction of such engineering systems. Consequently, engineering controls alone cannot provide complete protection from worker exposure to pesticides.

The need for a program that includes both engineering and work practice controls is illustrated by the 1976 pesticide overexposure cases in California's manufacturing and formulating plants. Of the 18 cases for which the manner of exposure could be determined, 6 resulted from open operations and could have been prevented by enclosure or ventilation. The other 12 cases involved escape of pesticides during leaks, ruptures, maintenance, sampling, or clean-up operations [297].

An effective work practices program encompasses many elements. For example, monitoring the workplace environment and workers' health can provide data necessary to plan and evaluate

control methods. Protective clothing and equipment, if properly selected, used, and maintained, can isolate workers from exposure to pesticide chemicals. Housekeeping, sanitation, and hygiene practices include methods to segregate, collect, and dispose of fugitive pesticide materials to further prevent worker exposure. Provisions for dealing with emergencies are also a necessary part of the work practices program. Work practices are supported by labeling, posting, and training to inform personnel of pesticide hazards and of the procedures that protect against such hazards. Good supervision provides further support by ensuring that the work practices actually do protect workers from exposure.

Monitoring

As described in Chapter III, there is great variety in the toxic effects of pesticides, in the forms in which pesticides are made and handled, and in the operations employed in pesticide manufacture and formulation. Development of an effective program to control worker exposure to pesticides often involves a selection among alternate means of control. For instance, the physical properties and concentrations of airborne pesticides affect the choice of ventilation and enclosure methods. The chemical reactivity and physical form of pesticides indicate what types of personal protective equipment should be selected. The plant layout and movement of pesticides through it determine the type and scheduling of plant housekeeping. The state of health and exposure experience of workers limit their work assignments and the protective equipment they can wear.

Such choices are crucial. A wrong decision can lead to overexposure against which protection was intended. The following examples highlight the need to have adequate information in order to provide correct methods of exposure control for a particular situation. In one case, a production worker was wearing goggles while repairing a pesticide milling machine. His goggles were not dust-tight and both of his eyes were exposed to parathion [297]. In another case, a formulating company using mevinphos issued protective work clothing to its employees, but the clothing was of an improper type for protection against OP pesticides. Seven workers experienced mevinphos poisoning [29]. In another mevinphos incident, a worker with an abnormally low red blood cell (RBC) cholinesterase (ChE) level was assigned to fill cans with mevinphos and he experienced mevinphos poisoning [29]. In the case of a pesticide and fertilizer processing company, materials were stored away from the production area to minimize worker exposure. However, ammonium nitrate (an explosive) was warehoused so near to parathion, dicofol, and other pesticides that its explosion may have spread the pesticides over a wide area. A fire in the plant brought that hazard to the attention of state officials [305]. One pesticide formulator used ventilation as a protective measure in its cylinder-filling area. The company chose to use general ventilation when local exhaust ventilation would have been more appropriate for the packaging operation. As a result, a worker engaged in filling was overexposed to chloropicrin [29]. By monitoring both the pesticide and the worker in terms of their

interactions, information is obtained regarding actual and potential worker exposure. The monitoring data can then be used to select and to apply engineering and work practice controls appropriate for each pesticide manufacturing or formulating operation.

(a) Pesticide Monitoring

In the course of manufacture and formulation, pesticide chemicals move through various operations and undergo changes in form and concentration. The nature and quantity of pesticide to which workers may be exposed vary within each plant and from one plant to another. Providing protection attuned to each variation requires monitoring the pesticide in both normal processing operations and in those situations where it escapes from those operations.

(1) Pesticides in Processing

An initial pesticide plant survey should include an inventory of those pesticides present, and the physical, chemical, and toxicological properties of each. Besides aiding management in its selection of protective measures, this information may be required by physicians treating exposed plant workers or firemen fighting plant fires. A common practice is the delivery of an active ingredient to a formulator with specifications for formulation but with no further information on the pesticide itself. The formulator may be ignorant of the composition, properties, and hazards of the pesticide active ingredient [8(p 15)].

The survey of pesticide processing should follow the

materials as they move through the plant. Locations and types of equipment within the plant where pesticides are present should be noted so that adequate posting and labeling can be done. The monitoring of pesticides throughout the plant includes surveying pipes, troughs, and conveyors which carry pesticides within the production area. Nonenclosed operations and sources of potential leaks, as discussed in Chapter IV, should be identified to initiate environmental monitoring. Locations of pesticides within the plant layout will also be used to determine emergency escape and rescue routes.

Pesticide plants should be surveyed on a continuing basis. Changes in processing methods, variation in products, and fluctuations in material quantities used and stored all affect the potential for exposure to pesticides.

(2) Pesticide Emissions

The working environment should be monitored to determine the amounts and distribution of pesticides that have escaped into the workplace. This provides a measure of how and where engineering controls have failed to contain pesticides, and also indicates work practices that are necessary to prevent further exposure. Essentially, such monitoring means maintaining a day-to-day awareness of where exposures may occur from emitted pesticides within a plant. Work practice controls dependent on monitoring include selecting respirators and determining where workers can safely eat and drink.

Monitoring may include workplace air and surfaces. Various sampling methods are available for monitoring, but the

predominant consideration must be to measure pesticides to which workers are potentially exposed. Airborne pesticides can be sampled by collection devices worn by employees, with the device intake located within the breathing zone, though this may not always be practical. For airborne particulate pesticides, respirator filter pads have been used as sampling devices [306]. Pesticide contamination of surfaces can be sampled with wipe tests [307], using an absorbent material to soak up pesticide from handrails, furniture, etc, or with dermal pads, ie, absorbent swatches worn on the outside of workers' clothing, [306]. For pesticides that are difficult to sample or to analyze, a labeling material may be added for ease of monitoring. Fluorescein dye, for example, has been used to label hazardous materials to study their dissemination [307]. Relatively innocuous materials such as glycerin may be used to simulate the behavior of hazardous substances during their processing.

Environmental monitoring data should be recorded and maintained for use with other monitoring data. The correlation of airborne concentration data with medical examination reports may be very useful in identifying pesticide exposures.

(b) Worker Monitoring

Many work practices are effective in protecting a worker from exposure only when he follows specific behavior patterns in performing his assignment. Selection of specific work practices calls for an analysis of how and where various operations are carried out. Evaluation of whether work practices are being used to afford adequate protection requires an assessment of the

employees' state of health. Knowledge of job characteristics and physical capabilities of workers provides a basis for assigning workers to jobs where they would be least vulnerable to the effects of exposure.

(1) Worker Tasks

The object of task monitoring is to determine at what points exposures to pesticide may occur in a given job. If possible, a worker should be rerouted if his assignment requires his passing through a pesticide-contaminated area; in any case, he should always be apprised of the hazard. When a job requires opening pesticide systems to sample or to perform maintenance, the appropriate personal protective equipment must be used. The scheduling of jobs affects time at risk of exposure and may determine whether a worker has time to put on protective equipment before commencing work, or to shower after work. All of these aspects must be monitored to determine work practice controls.

The pesticides with which each worker may have contact must be identified. This determination is important in deciding how the worker is to be trained and what types of medical and biologic tests should be used.

(2) Worker Health

The demands and risks of working in pesticide manufacture and formulation require a level of fitness in workers which should be determined in a preplacement examination, and results should be used by the physician with regard to proper placement of the employee. Such examinations can be used to

detect disabilities such as deafness which could impair a worker's ability to protect himself, predisposing conditions such as allergies or pregnancy which could make individuals more susceptible to pesticide effects, illnesses such as cirrhosis or pulmonary disease which could aggravate the effect of pesticide exposure, occupational disease from past exposure to other pesticides, toxicants, or irritants, and cardiopulmonary or psychologic problems which could preclude a worker from using a respirator. The preassignment physical also provides an opportunity to establish the baseline levels of an employee's health before any exposure to pesticides occurs. Baseline levels can be used to compare pre- and post-exposure health aspects such as regularity of menstruation, or to compare specific pre- and post-exposure laboratory testing parameters such as blood ChE activity. In assessing the prospective employee's general health, it is important to be aware of other health aspects that may synergistically amplify the potential adverse effects of contact with pesticides. These include tobacco smoking and the use of alcohol, medications, and other drugs, such as caffeine in coffee.

One other significant but often overlooked purpose of preplacement physicals is counseling employees to be aware of their own states of health. A worker informed of the symptoms and effects of pesticide exposure may discern his own health problems as well as those of coworkers at an earlier stage.

Periodic physical examinations with appropriate biologic testing provide a continuing assessment of employee health and

indicate whether a change in job assignment is necessary. Such exams may detect worker exposures by measuring pesticide chemicals or their metabolites, or by identifying the effects of exposure.

Unscheduled exams should also be administered when unusual circumstances arise. Any worker sustaining an illness or injury symptomatic of pesticide poisioning should be examined to determine attributability to pesticide exposure. Conversely, any worker who has been or is suspected of having been overexposed to a pesticide chemical should be examined to determine the effects and need for medical treatment. EPA has published a guide for treatment of overexposure to various classes of pesticides [36].

(A) Medical Monitoring for Level of Exposure

Two levels of screening must be considered in developing standards for medical monitoring: a determination of whether there has been an absorption of unacceptably high quantities of pesticide, and an analysis of any signs and symptoms of pathologic processes resulting from excessive exposure. Selection of monitoring techniques and interpretation of results will vary with the level of screening, the particular pesticide or pesticide class, and the target organ(s) potentially involved.

Environmental monitoring cannot quantify the true hazard where exposure is primarily through skin contact, or where exposure control is dependent on personal protective devices being in place and functioning properly. For those pesticides

that carry a high risk of systemic effects, eg, lead compounds, it may be more valuable to monitor workers for absorption of the pesticides rather than to perform extensive tests for the pathologic effects of the pesticides. Such tests for the body burden of a pesticide can give results that are more quantified and more easily comparable to baselines and group results than are clinical tests. Where possible, of course, it is preferable to be aware of both the absorption and the effects. Biologic monitoring has the advantage of usually detecting hazardous exposure levels before clinical effects are evident. A disadvantage of biologic monitoring is that it can miss intermittent overexposure. A biologic monitoring program must include consideration of (1) the availability of analytic techniques for various pesticides, their metabolites, or indices of their biologic effects, (2) the cooperation of the workers in providing samples, ie, the results of the program must not be seen as punitive in nature, and (3) the determination of the concentration of a pesticide or its metabolites in biologic fluids, or the changes in other indices of exposure that identify potentially hazardous exposures. In the absence of medical criteria for pesticide burdens, each worker's level should be compared with the mean level for all the workers monitored and to his mean from previous biologic monitoring periods. The probability of all workers being overexposed and, therefore, each being "acceptably" close to the mean cannot be ignored but must be interpreted by the physicians at their discretion.

In the case of those pesticides for which biologic

monitoring is feasible, the scientific literature [308] provides discussion of which body fluids or tissues are most reliably or practically analyzed for the presence of pesticides or their metabolites. In some cases, the higher sensitivity of blood analysis is unnecessary, because acceptable blood levels may produce measurable quantities in the urine. In these instances, urinalysis would be preferred since urine collection is far more acceptable to the employee than is venipuncture.

Although employee exposures should ideally be measured by environmental (workplace air) monitoring, percutaneous exposures which are significant with pesticides may be assessed by biologic monitoring. The choice of biologic tests should avoid invasive tests, eg, blood sampling, when possible, but not at the risk of using a method which is inaccurate or may miss significant exposures, eg, observation of pupillary dialation as an indicator of overexposure to organophosphorus compounds (OP's). In no event should biologic monitoring be depended upon as a substitute for engineering controls and work practices.

(B) Medical Monitoring for Effects of Exposure

A variety of effects of pesticides on humans have been determined from case studies, epidemiologic surveys, and extrapolation of animal data. Each effect involves a target organ for which clinical evaluation criteria have been developed, consisting of symptoms (history), physical examination, and laboratory data. Although a thorough history and a focused physical examination will permit an examining physician to

determine the presence of most pathologic processes at some point in their evolution, laboratory studies are necessary for early determination of dysfunction or disease for the organs that are relatively inaccessible and that have a high degree of functional reserve.

In the screening aspect of a medical program, the anticipated worker's acceptability of each recommended laboratory test must be balanced against the test's sensitivity, the seriousness of the abnormality to be detected, and the probability of the abnormality's developing from pesticide exposure. Furthermore, tests are chosen for simplicity of sample collection, processing, and analysis wherever possible. In many instances, tests are used because they are easy to perform and are sensitive, although they are not necessarily specific. If the results are positive, another more specific test would be requested. The choice of tests should be governed by the particular pesticide(s) to which a worker is exposed. A complete medical history and physical exam (including a thorough neurologic exam) are required regardless of the pesticide involved because of the probability of undiscovered effects. Appropriate laboratory tests and elements of the physical examination to be stressed are described in the following paragraphs according to target organ systems.

(i) Skin

Pesticides are known to produce a variety of symptoms related to the skin. The clinical syndrome falls into the two broad categories of dermatitis: contact

irritation and sensitivity reactions, as discussed in Chapter III.

Skin sensitization does not occur on the first exposure but may occur after several weeks or many years of pesticide contact [138]. Sensitization may occur after either skin contact or inhalation. Although the process is more likely to occur after prolonged exposure at high concentrations, subsequent allergic responses can result after exposure at very low concentrations. Patch testing can be most useful as a diagnostic aid where a worker who routinely comes into contact with several pesticides has developed symptoms of skin sensitization. However, patch tests used as a preplacement screening technique may cause senitization in the employee. As with contact irritants, skin sensitization potential is best determined by medical history and physical examination.

(ii) Liver

Liver toxicity is a well-documented effect from absorption of chlorinated hydrocarbons and chlorinated organic acids [121,122,124]. Because of the liver's vast reserve functional capacity, only acute hepatotoxicity or severe cumulative chronic damage will produce recognizable symptoms. These include nausea, vomiting, diarrhea, weakness, general malaise, and jaundice.

Numerous blood chemistry analyses are available to screen for early liver dysfunction. The tests most frequently employed in screening for liver disease are serum bilirubin, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic

transaminase (SGPT), gamma glutamyl transpeptidase, and isocitric dehydrogenase. Preplacement physical examination, laboratory studies, and a thorough social history are important in order to rule cut liver damage from excessive alcohol consumption or other previcus conditions.

(iii) Kidney

Impaired renal function can result from chronic exposure to various pesticides, including carbaryl [105], methyl bromide [127], mercury compounds [129], and pentachlorophenol [131]. Screening for kidney dysfunction can be accomplished by measurement of blood urea nitrogen (BUN) and serum creatinine and by urinalysis for presence of protein, glucose, castes, and cells [308].

(iv) Respiratory

Besides providing a route for absorption of pesticides by inhalation, the respiratory system is itself subject to toxic effects from pesticide contact during breathing. Local irritation may occur in the sensitive mucosa of the nose, mouth, throat, trachea, and bronchi. More severe effects include pulmonary fibrosis, emphysema, and bronchopneumonia. Symptoms can be acute, usually resulting from accidental inhalation exposure, although other routes of exposure have been implicated. Paraquat has caused pulmonary fibrosis in humans [150]. Exposure to a copper sulfate-lime pesticide spray caused hystiocytic granulomas and nodular scars [125].

In the absence of acute symptoms, physical examination is not likely to detect early pulmonary fibrosis or asymptomatic

emphysema. X-ray examination of the chest and pulmonary function studies (spirometry) are recommended as screening tests for detection of pulmonary fibrosis and emphysema. Baseline (preemployment) studies are imperative for the proper evaluation of changes due to pesticide exposure. Lower respiratory secretions (sputum) may be collected for cytologic examination. Some pesticides have been implicated as being carcinogenic in humans [98,167], especially arsenic compounds which appear to increase the occurrence of respiratory cancer [48]. Sputum cytology has been recommended as a means of detection of pulmonary carcinoma in high-risk groups [82] and is required by the Occupational Safety and Health Administration (OSHA) in its Coke Oven Standard.

(v) Eye

Most eye effects from pesticides are acute chemical injuries resulting from accidental spraying, splashing, or contact with dusts. An important exception is the risk of cataract production from pesticides such as dinitrophenol [51] and dinitro-o-cresol [309]. Screening procedures for cataracts include testing of visual acuity with corrective lenses in place and ophthalmoscopic examination.

(vi) Blood

Both anemia and leukopenia have been associated with pesticide exposure. Reported cases have implicated chlordane [151], lindane [158], and dichlorodiphenyltrichloroethane (DDT) [153]. Anemia may be suspected when there is a history of fatigue with physical

findings of pallor and tachycardia, but the definitive screening test is a complete blood count (CBC) which includes determination of hemoglobin concentration, hematocrit, white blood cell count, and white blood cell differential count.

(vii) Heart

Cardiac abnormalities, which have long been associated with arsenic poisoning, have been reported in workers chronically exposed to arsenical pesticides. Changes in the electrocardiogram (ECG) of prolonged Q-T interval and flattened T-waves are associated with arsenic toxicity [310]. Richardson et al [165] reported higher systolic blood pressure among workers exposed to DDT. Exposure of workers over the age of 40 to OP compounds may increase their risk of cardiac failure [163] due to vascular changes and changes in the ability of the blood to coagulate (GE Quinby, MD, written communication, May 1978).

(viii) Reproductive System

Recent findings of infertility in male workers exposed to DBCP have demonstrated the necessity to monitor sperm counts in workers exposed to dibromochloropropane (DBCP) and to other pesticides such as Kepone which have shown effects on reproduction in animals. Studies performed on workers exposed to DBCP demonstrated a correlation between oligospermia and elevated blood levels of follicle stimulating hormone (FSH) and luteinizing hormone (LH) [119].

(ix) Nervous System

The most frequently reported human

health effects of pesticide exposure are those related to the nervous system. Symptoms cover the full range from headaches and tremors to epileptiform convulsions [33]. Behavioral problems attributed to chronic pesticide exposure range from anxiety and depression to hallucinations and schizophrenia [43,44]. Compounds from nearly every pesticide class have been demonstrated to have neurotoxic effects either on the central nervous system (CNS) or on peripheral nerves. Medical monitoring for neurotoxic effects must include a thorough history and neurologic examination.

Acetylcholine transmits nerve impulses to the heart and other cholinergically innervated muscles and other effectors. This kind of transmission is terminated by hydrolysis through ChE's of the acetylcholine released from nerve endings. OP and carbamate pesticides are known inhibitors of ChE's. The inhibiting effect of these pesticides may be measured by determination of ChE activity in the blood plasma and RBC's [97]. Although carbamates inhibit ChE activity, their effect is usually brief and reversible. The duration of ChE depression due to OP pesticide exposure makes periodic monitoring of ChE activity a useful tool to detect occupational exposures [311].

The monitoring requires establishing a baseline for each worker, because normal values may vary greatly from one individual to another. RBC ChE activity should be determined for workers exposed to OP insecticides. Measured values of ChE activity determinations can vary due to when blood is sampled, the laboratory used, and the method employed. Some of the more

widely used and accepted methods are Modified Michel, pH Stat, and Ellman (see Appendix II). In addition, some OP and carbamate insecticides preferentially inhibit plasma ChE. Monitoring of plasma ChE activity should be considered by the physician for those employees exposed to such OP insecticides [311].

Several researchers have suggested that electromyography and electroneurography may have use as indicators of functional myoneural disturbances in the absence of depressed ChE activity [32,33,43,115,116].

(C) Frequency of Medical Monitoring

Medical exams and biologic tests must be administered frequently enough to detect occupational illness, ideally before the exposures induce any deterioration of health. However, several factors limit frequency of monitoring. Expense to employers and acceptability to employees are significant administrative considerations. From a health standpoint, some tests and examination methods pose a health hazard which must be weighed against the exposure hazard being screened. Drawing blood can carry some health risk, and X-ray examination exposes workers to radiation.

It is common practice to decrease the interval between physical exams with increasing worker age. One major manufacturer of pesticides gives mandatory physicals to workers less than 45 years of age every 1.5 years, and annually to workers over 45 years of age [312]. A large formulator of pesticides requires exams at ages 25, 30, 35, 38, 40, and annually thereafter [313].

Besides employee age, job assignment may determine how frequently total physical examinations or particular biologic tests are given. Workers in high-risk occupations such as pesticide packaging should be examined at least annually. Employees who work with OP pesticides may require blood ChE tests as often as weekly [297].

Recent studies have indicated several alternatives in selecting the frequency of medical monitoring. One plan would require very infrequent mandatory exams (every 5 years), with exams offered voluntarily every year. Another alternative proposes 2- to 5-year intervals for asymptomatic workers, with exams being given whenever a worker believes he has been exposed. This, of course, requires training workers to recognize signs and symptoms of pesticide intoxication.

The frequency of biologic testing and periodic exams should be related to the period of time in which the pesticide could cause adverse effects as well as the severity of the effects.

Personal Protective Clothing and Equipment

In 1975, there were 94 reported cases of occupational illness resulting from exposure to pesticides or their residues in manufacturing and formulating facilities in California. Exposed were 54 production workers and 40 workers who were cleaning or repairing pesticide-handling equipment. Exposures were due to inhalation, ingestion, and skin or eye contact with the pesticide chemicals [29]. Where engineering controls, as discussed in Chapter IV, are inadequate or infeasible, other

methods of protection must be used. Use of personal protective equipment and clothing provides another means for reducing occupational exposures by isolating the worker from the pesticide. However, it must be emphasized that the use of personal protective clothing and equipment will not by itself prevent pesticide poisoning and should not give the worker a false sense of security. Various types of protective equipment and clothing are discussed below.

(a) Protective Clothing

In the manufacture and formulation of pesticides, many opportunities can arise for unintentional direct contact of the pesticide with the worker. Liquids can be splashed or spilled onto the worker's skin or into his eyes. Dusts may be blown into the worker's eyes or mouth. Engineering controls alone are not always sufficient to prevent these occurrences. Therefore, direct protection of the routes of entry by use of protective clothing should help reduce these exposures. In an incident describing the effectiveness of protective clothing, a worker who was filling and capping drums of mevinphos had some of the chemical splashed on his arm [29]. Because he was wearing protective clothing at the time, he had very little skin exposure and only experienced mild symptoms of overexposure. Violations cited by OSHA in pesticide plants have included lack of proper protective clothing; workers involved in pesticide manufacture and formulation have risked exposure to parathion, chlordane, and dichlorvos because of inadequate protective clothing and equipment.

Wolfe and Armstrong [18] studied the effectiveness of personal protective equipment in two DDT formulation plants. Calculations were made to estimate the maximum potential exposure that could occur in different work situations where protective gear was not used. Potential exposure was calculated assuming that a worker wore an open-collar sleeveless shirt, no respirator, no hat, and no gloves. These exposure values were compared with the actual values obtained, taking into account the protective clothing and respirators actually worn by the workers. Workers in both formulating plants wore rubber boots, caps, respirators, long-sleeved cloth coveralls open at the neck, and rubber gauntlet gloves, which provided some protection at the wrist area not covered by the sleeve. In plant A, the caps worn were the type with a bill at the front. The bill was considered to give some protection from downward-moving particles in the face-front area, but very little protection on other face-neck areas. In plant B, the caps worn were beanie-type with no bill and provided protection only for the top of the head. Rubber aprons were worn in plant B, and that plant also had better ventilation and other engineering controls. Exposure values were calculated for each worker, taking into account the estimated percentage of skin area actually exposed. By comparing the mean values of toxic dose received per hour with those calculated for the theoretical "minimum protection" exposure, it was calculated that had the workers not worn their protective equipment they would have been exposed to 5-10 times more DDT in plant A and approximately 2.5-3.5 times more DDT in plant B.

Protective clothing ranges from gloves and aprons to garments that completely cover the body. There is also a diversity of materials used in these clothes including rubber, leather, cloth, and synthetic fibers. Because of the many types of clothing and material available, selection of proper protection should be carefully considered. Probably the most important criterion for selection is the degree of protection which a particular piece of equipment affords against a potential hazard. This should take into account the physical form of the pesticide chemical, ie, solid, liquid, or gas. For liquid formulations, or wet hygroscopic solids, this is particularly important, because of the possibility of permeation through the clothing worn. Although cloth coveralls provide a reasonable amount of dermal protection, the wearing of waterproof trousers provides the best protection for the lower trunk and leg areas and is especially recommended in work situations where there is a chance of liquid spillage or penetration due to excessive contact with dry pesticides. For gases such as methyl bromide, the use of gloves may cause the volatile gas to be trapped next to the skin surface and thereby increase absorption (J Conder, written communication, February 1978).

To be effective, protective clothing must be impervious to the chemicals it is protecting against. However, impervious clothing may interfere with the body's cooling mechanism by excluding airflow to the skin surface. The effects of different types and weaves of cloth vs their effect in minimizing the penetration of residues contacted in the field has been examined.

Six orange pickers participated in the study wearing 2- x 3-inch patches of tightly woven cotton shirting fabric. The patch was backed up by aluminum foil in order to trap the residues which penetrated. The results of this initial study indicated that 47% of the applied dose of parathion and its more toxic oxidation product, paraoxon, penetrated the tightly woven cotton material. The California State Department of Health recommended the use of nonwoven laminar treated clothing with treatment on both sides of spun-bonded polypropylene. The advantages of this material are that it is lightweight, disposable, and cool to wear in hot weather [314].

Davies [315] reported a study in which silicone was used to treat the clothing of pesticide workers. Shirts, pants, socks, and shoes were dipped in a silicone solution. By measuring metabolites in the urine, it was determined that workers with treated clothing sustained less skin exposure to parathion than those with untreated clothing.

Although protective clothing should be selected for its resistance to chemical penetration, truly impermeable clothing may be difficult to find. In testing various protective glove materials for permeability, Sansone and Tewari [316,317] found that penetration of all materials used occurred with all pesticides tested. Carbon tetrachloride, methylene chloride, tetrachloroethane, trichloroethane, and perchloroethylene substantially (10% or more) penetrated natural rubber, neoprene, and polyvinyl chloride (PVC) glove materials within half an hour. Polyvinyl alcohol (PVA) glove material showed much greater

resistance to chlorinated pesticides, but it was penetrated by DBCP and EDB, as were the other materials, in as little as 5 minutes. Only acrylonitrile failed to penetrate each material in 5 minutes, but penetrated all three materials within 30 minutes.

Even when wearing protective clothing, care must be taken to prevent gross contamination from excessive amounts of chemicals. A worker manifested signs of mevinphos poisoning after he leaned against a spout that was used to fill containers with that pesticide. Some of the liquid soaked through his protective coveralls [29]. An OSHA inspection of one pesticide formulator revealed contamination of personal protective clothing by baygon and by sodium arsenite.

Protective clothing should not be worn home or taken home to be laundered. Cleaning should be done at work with appropriate safeguards, or by a professional laundry. This prevents workers from carrying residual chemicals home on their clothing and thereby possibly exposing their families. Despite washing, pesticide chemicals may remain on clothing. Southwick [318] reported one fatality attributable to work clothing that remained contaminated with parathion even after laundering.

Urry et al [319] compared the effectiveness of a common chlorine bleach solution in the removal of pesticides from two fabrics at two different soak periods. The pesticides used were parathion, diazinon, lindane, and carbofuran. The two fabrics, typical of work clothing, were 100% cotton denim and 50/50% polyester/cotton. The stock bleach solution was 5.25% sodium hypochlorite laundering bleach, diluted with water for a final

chlorine concentration of 0.05%. Each of the 4 pesticides was applied to the fabrics and each fabric was subjected to the bleach solution for 1 or 24 hours, respectively, for a total of 16 experiments. In denim fabric, after a 1-hour soak, 41.4% parathion, 49.6% diazinon, 21.2% lindane, and 32.5% carbofuran were removed, and after 24 hours, 98.8% parathion, 93.6% diazinon, 14.8% lindane, and 95.0% carbofuran were removed. In polyester cotton, after 1-hour soaks, 41.2% parathion, 60.9% diazinon, 19.0% lindane, and 72.5% carbofuran were removed; and after 24 hours, 96.4% parathion, 98.6% diazinon, 17.1% lindane, and 100% carbofuran were removed. The authors concluded that a 1-hour soak in 1% chlorine bleach alone was not sufficient to remove some types of pesticide contamination; however, after a 24-hour soak, removal was quite good, except for lindane. They suggested that combinations of bleaching and soap laudering would be more effective in pesticide removal than using bleach alone.

Protective clothing should be kept separate from street clothing so that contamination of street clothing will not occur. The clothing should be inspected frequently for rips or tears and repaired or replaced when so indicated.

(b) Gloves and Gauntlets

Dermatitis and absorption of chemicals through the skin are two main problems associated with the handling of pesticides. Gloves and gauntlets are specialized types of protective clothing designed to protect the hands and forearms from contact with pesticide chemicals, thereby reducing exposure of the skin.

Handling pesticide chemicals or their containers with

gloves reduces exposure to leaked pesticides, especially those which may penetrate the skin. A foreman taking a sample accidentally popped a lid on a vial and spilled mevinphos on his hands [29]. Even though he washed immediately, he still developed stomach cramps. Another worker was hospitalized for 3 days and was treated for OP poisoning after using his bare hands to put the cap back on a mevinphos sample container [29]. In both of these cases, gloves were provided and required for taking the sample but had not been worn. One employee developed dermatitis on her hands and forearms after filling bottles with malathion [29]. She had refused to wear rubber gloves that were provided.

Gloves should be checked before each use to ensure that they are not damaged or contaminated on their inside surfaces. A batch maker in a formulation plant, who was wearing gloves, spilled a fungicide on his hands and developed contact dermatitis [297]. The accident report surmised that either the gloves had a hole in them or some of the chemical spilled into the top of the gloves. Inspection of the gloves might have prevented the exposure.

(c) Foot Protection

Protection of feet requires specialized types of protective clothing in the form of shoe coverings or boots. This is especially important where liquid pesticide chemicals are handled. First and second degree chemical burns were sustained by a production operator who was not wearing any foot protection when he spilled ethylene dibromide on his foot [297]. Wearing

rubber boots might have prevented this accident.

If foot protective devices become contaminated, they should be decontaminated or replaced. A foreman who spilled ethylene dibromide into his boot washed his foot and then put the contaminated boot back on [320]. Chemical burns and dermatitis of his feet resulted.

Boots and other foot coverings need to be examined or a regular basis for any holes or breaks that would permit leakage of pesticide chemicals. When not in use, protective footwear should be stored in areas free from contamination.

(d) Head and Face Protection

Many different types of protective equipment are available for preventing exposures of the face and head to pesticide chemicals. These include safety glasses, goggles, face shields, and various types of hats.

Protection of face and head is important, considering the different sites and routes of exposure to pesticides. According to one study [20], the human body absorbs parathion at rates that vary from 32% for the scalp to 47% for the ear canal, to an estimated 100% for the eyes (see Table III-1). During 1975 in California, 8 out of 56 (14%) production workers and 15 out of 40 (38%) maintenance men who experienced occupational illnesses due to pesticides received eye exposures [321].

Head protection is important where exposure from overhead sources is likely to occur. A helmet with a brim all the way around provides the most complete protection for head, face, and back of the neck. Protective caps which completely cover the

hair are necessary for two reasons. First, they prevent exposure of the scalp, and second, they keep pesticides from being retained by the hair and later falling into the eyes, or acting as a continuous source of dermal exposure. Headgear should be cool and lightweight so that it is comfortable for those wearing it.

Each job should be evaluated for the possible exposures that could occur and protective equipment chosen accordingly. If there is a danger of liquids being splashed into the face, a face shield should be worn. Splash-proof goggles will prevent liquids or dusts from getting in the eyes.

Care must be taken in selecting protective equipment lest it provide a false sense of security. Workers wearing inadeguate equipment might not realize that they are being exposed if they think they are wearing the proper equipment. Maddy and Topper [29] cited two cases where workers were wearing safety glasses instead of goggles, and eye injury occurred. In another case, a worker had captafol powder blown into both his eyes through the side vent of his goggles. In each of these cases, exposure could have been prevented by better job evaluation and selection of appropriate equipment. One employee had liquid lime sulfur splashed into his face [29]. Although the use of safety equipment was not required by the employer for the job he was performing, a face shield might have guarded against such exposure.

Maddy and Edmiston [297] cited two cases where eye contamination occurred because no protective equipment was worn.

In one case, a supervisor had "ant powder" blown into his eyes while trying to repair a packaging machine. In another instance, a can of insect spray exploded and sprayed pesticide into the eyes of the machine operator.

When selecting protective equipment for the face and head, different configurations and construction materials are important factors. Plastic lenses are more resistant to breakage and hot materials, and take longer to fog than most glass. Plastic also weighs less, which aids in wearing comfort. If equipment is not comfortable, workers will resist wearing it. One worker had propargite sprayed into his eyes after he removed his goggles [321]. It was a hot day and the goggles irritated the skin around his eyes.

If a worker needs corrective lenses, it is preferable to grind the correction into a goggles lens [322]. Where this is not possible, special goggles that fit over glasses are required. Although considerable controversy exists regarding the wearing of contact lenses during chemical exposure, contact lenses should not be worn because of the possibility of getting contaminants, particularly liquids and vapors, caught between the contact lens and the eye, which may result in severe chemical burns. However, if goggles containing corrective lenses substantially reduce the employee's vision, contact lenses may be worn under splash-proof chemical goggles.

Face shields, which attach to head gear, are designed to give protection to the entire face from the forehead to the neck. They are used mainly where splashing of liquid pesticide

chemicals is likely to occur.

When not in use, protective equipment should be stored in areas free from pesticide chemical contamination. If equipment were left in a place where it became contaminated, it could become a source of exposure for the next user. Before using protective equipment, each worker should ensure that it is clean and that is has not been damaged in any way that would prevent proper functioning.

(e) Respiratory Protective Equipment

Cases of occupational illness and death have been attributed to lack or improper handling of respirators and to improper guidance as to respirator use in pesticide facilities. De Palma [113] reported three cases of exposure to arsine due to nonuse of respirators in a plant producing the herbicide sodium acid methane arsenate.

Kazantis et al [106] cited another incident in which respirators were not used and overexposure occurred during the mixing of aldrin with fuller's earth. The employee's exposure might have been reduced by engineering controls, but in the absence of such controls, a much more effective type of respirator should have been used.

In the above-mentioned incidents, proper assessment of the hazard could have led to providing appropriate protection to the workers. Hazard control, as previously mentioned in Chapter IV, should start at the process, equipment, and plant design levels to control contaminants at their source.

(1) Respirator Selection and Limitations

Respiratory protection devices vary in design, application, and protective capability. The user, supervisor, and employer must therefore assess the inhalation hazard and understand the specific use and limitations of available equipment to assure proper selection.

Respiratory protective devices are tested and approved by NIOSH and the Mining Safety and Health Administration (MSHA) for protection against a wide range of inhalation hazards, including oxygen-deficient and highly toxic atmospheres and those containing "nuisance" dusts. Whenever possible, it is desirable to select NIOSH/MSHA-approved equipment. Testing and approval of these respirators are subject to conditions in 30 CFR Part 11.

In addition, 29 CFR 1910.134 states that respirators shall be selected on the basis of the hazards to which workers are exposed and that ANSI Z88.2-1969 shall be used for guidance in this selection. Many of the criteria for selection of respirators, including the joint NIOSH/OSHA decision logic for respirators [323], are dependent on permissible exposure limits and therefore cannot be applied to substances for which Federal standards have not been established. Both the ANSI standard and the NIOSH/OSHA decision logic use other criteria in addition to exposure limits for deciding respirator use, including the possibility of skin absorption, poor warning properties, and eye irritation by the material. The following are guidelines suggested in these criteria [323]:

(A) Supplied air suits provide both skin and respiratory protection and should be used in handling

extremely toxic substances which may be absorbed through the skin.

(B) Only full facepiece respirators should be used when contaminants may produce eye irritation.

(C) For firefighting, the positive pressure, self-contained breathing apparatus should be used.

In some industry segments [8(p 82)], chemical cartridge and canister masks are not used and positive-pressure air supplied respirators are preferred. Two types of the latter are available: self-contained breathing apparatus and air-line respirators. These air-supplied respirators can be safer than chemical cartridge or canister mask respirators. When the positive-pressure type of air-supplied respirator is worn, facepiece leaks will simply allow air to pass out of the facepiece rather than into it. The worker is not dependent on the surrounding air which may be a source of a pesticide or other contaminant, thus further decreasing chances for exposure. If there is an oxygen-deficient atmosphere, such as may occur in a reaction vessel, only self-contained equipment should be used [324].

The protection afforded by any respiratory device is limited by the quality of the seal between the respirator facepiece and the wearer's face. Facial seal, and therefore, respiratory fit, can vary due to a variety of factors, such as the facial contour, the way the respirator is donned each time it is used, the amount of perspiration on the face, the amount of beard growth, the tightness of the straps, and other factors. A

study in 1973 [325] indicated that both daily growth of facial hair as well as established beards detrimentally affect the seal of respirators.

The use of eye glasses also affects the facial seal of respirators, and wherever glasses penetrate the seal, a leak and resultant loss of protection will occur. Various ways of preventing this leakage have been utilized, including mounting the glasses inside the facepiece. The use of contact lenses is not a good solution to this problem. If a contact lens should happen to slip or need adjustment while the respirator facepiece is being worn in a hazardous atmosphere, a serious problem would exist since removal of the respirator would not be possible and immediate escape from the atmosphere may not be possible either.

A limitation of air-purifying respirators is that the end of service life for a cartridge or canister is not always evident. In formulating and manufacturing areas, inherent problems arise when odor detection is used as a sign of exposure because some contaminants do not have detectable odors. Also, the odor threshold may be higher than an established permissible exposure limit, or the odor of the contaminant may be masked by other airborne substances.

Another major limiting factor in wearing respirators is the breathing resistance inherent in many respirators, such as the canister type. Respirators approved under 30 CFR Part 11 have inhalation resistances varying from 12 to 102 mm of water and exhalation resistances varying from 15 to 25 mm of water; these respirator performance specifications are for normal, healthy men

[325]. Pulmonary disease, the resistance to airflow in respirators, and pulmonary function capability of "normal" healthy workers must be considered in evaluating whether employees can use respirators. In the case of self-contained breathing apparatus, weight of the equipment would also be a factor making the respirator difficult to use. If a worker's cardiovascular or pulmonary function is impaired, wearing a respirator may constitute an unacceptable risk due to breathing resistance and/or weight of the respirator apparatus itself. Also for all Group I pesticides, where respirators are necessary, a quantitative fit test should be performed to ensure that the employee is not exposed to pesticides as a result of substantial leaks.

(2) Respiratory Protective Equipment Care

If respirators are to be effective, they must have proper care. In one NIOSH site visit of a formulating plant [8(p 75)], respirators were sometimes dirty or lying on workbenches. This may lead to contaminated filters, cartridges, or facepieces, and potentially allow for direct inhalation of a pesticide. Certain respirator parts must also be handled carefully. Rubber facepieces become hardened and head straps lose their elasticity with age and exposure to heat and sunlight. These conditions lead to poor fit and allow leakage around the facepiece. Because the respirator may be used as a life-protecting system, the necessity for its proper maintenance must be emphasized to workers in respirator use training. Several pesticide formulators have been cited by OSHA for failure to have a

comprehensive program covering respirator use and maintenance. Such practices have potentially exposed workers to chlordane, Kepone, and phorate.

Two of the more common bad practices reported [327] are: (1) failing to wash the facepiece properly and (2) neglecting to change the filter cartridges or canisters regularly. Washing of the facepiece of a cartridge-type respirator should not be attempted while the cartridges are in place since moisture may contact the activated charcoal filter material. Merkle, at the National Conference on Protective Clothing and Safety Equipment for Pesticide Workers [328], suggested a procedure for cleaning respirators. The mask parts (with filters removed) and other protective gear should be placed in a 5% solution of sodium hydroxide or a strong alkaline soap solution for a minute or two, followed by a thorough rinse with clean water. Cleaning of the mask parts with a cleaner-sanitizer, such as ethanol, was also recommended. Solvent materials that affect rubber should never be used as cleaners because they may cause deterioration of rubber parts.

Proper maintenance and storage of respirators are also essential to a respirator's continuing effectiveness. Merkle [328] recommended that in the specific case of maintaining methyl bromide respirators, gas mask canisters should be replaced after each use because methyl bromide has poor retention characteristics in activated charcoal. After a few day's storage, a partially used canister will evolve methyl bromide even when clean air is passed through it and thus will become a

potential hazard in itself.

OSHA requires in 29 CFR 1910.134 that respirators be stored to protect against dust, sunlight, heat, extreme cold, excessive moisture, and damaging chemicals. In order to accomplish these objectives, the National Safety Council (NSC) has recommended [322] that freshly cleaned respirators be placed in heat-sealed or reusable plastic bags until reissue. They should be stored in a clean, dry location away from sunlight to protect against loss of elasticity. Storing a respirator in the position in which it is used also prevents distortion of the facepiece, which may cause a poor fit.

(3) Respirator Education

For safe and effective use of any respiratory protective device, the user should be properly instructed in its selection, use, and maintenance. Misuse can be avoided by establishing written procedures for respirator selection and use, and by properly supervising all aspects of a respirator program. The written procedures should contain all information needed to ensure proper respiratory protection of a specific group of workers against a specific hazard or several particular hazards. Description of the limitation of each device against different materials or concentrations helps the user select the proper respiratory protection. The proper use of respirators is highly dependent on thorough assessment of the hazard; otherwise the procedures will have only limited validity.

Another major element to be included in written procedures should be a detailed description for training workers in proper

use of the respirator, including fitting. Merkle [328] recommended that each worker have the capability to check for tightness before entering the exposure area. This can only be achieved by training the worker on how to properly wear respirators. Written procedures for cleaning and disinfecting respirators, repair of worn or defective parts, and proper storage instructions aid in reducing exposures.

Particularly important is establishing procedures for respirator use during emergencies such as fire, large spillage of volatile material, accidental release of a toxic substance, or failure of a ventilation system. Confusion that might occur in emergency situations may be alleviated by practice drills. Furthermore, these emergency procedures should be used in training emergency response teams. Location of respiratory devices in these situations is vital for safety of the worker.

Administrative procedures are also important in developing a respirator program. Control of inventory of spare parts, shelf-life information, and notation of dates for servicing ensure proper maintenance of respirators.

Proper issuance of respirators to ensure use of the proper one for a given hazard is another administrative task. Supervisory personnel should be given guidance in surveillance of respirator use and determination of worker's exposures to respiratory hazards. Simply having written procedures is not sufficient. Safety can be firmly established only by supervision to make sure that the proper respirator is being used and by periodic inspection and testing of respirators.

Housekeeping, Hygiene, and Sanitation

Cleanliness of the workplace and personal hygiene is essential to minimizing pesticide exposures. Pesticide accumulations in the working area can expose workers by skin contact when touching contaminated handrails, tools, equipment controls, and furniture, or by inhalation when moving air or vibrating surfaces cause reemission of pesticides into the air. Failure to cleanse pesticides from the skin may not only give rise to dermatitis but also may allow absorption through the skin to cause systemic effects. Contamination of foods, beverages, eating and drinking utensils, or smoking materials allows pesticides to enter the body by ingestion or inhalation.

Lack of cleanliness has been responsible for a variety of pesticide exposures. In one case, the outside surface of pesticide plant equipment was contaminated with a wet mevinphos residue. After contact with the dirty surface, the material soaked through to an employee's skin and he experienced OP poisoning symptoms [29]. Another pesticide exposure was attributed to contact with a worker's contaminated skin surface when a laboratory worker injured his eyes after rubbing them with his dichloropropane-contaminated hands [297]. In another case, the contamination of a drinking container with paraquat led to a fatal overexposure by ingestion [299].

(a) Plant Housekeeping and Disposal

The object of housekeeping in a pesticide manufacturing or formulating plant is to protect employees from pesticide

exposure; one way is to recapture spilled or leaked pesticides. This has a direct bearing on cleaning procedures. Flushing contaminated areas with a jet of steam, air, or water may serve only to further disperse the pesticide. For example, a worker accidentally contaminated his eyes with pesticide while using steam to clean pesticide-handling equipment [29]. Another worker, using a high-pressure air hose to flush pesticide, blew the material into his own face causing chemical dermatitis [29]. Surfaces should be washed down only if the runoff can be collected by drains or sumps and can be adequately decontaminated before disposal. Liquid pesticides can be cleaned up by covering with an absorbent such as clay. It is common practice among formulators to reuse the pesticide-soaked absorbent in making formulations [8(p 38)]. Solid pesticides should be cleaned up by vacuuming, but care must be taken that the vacuum system collector entrains respirable particles. Containers of collected waste pesticide should be handled and labeled with the same precautions given to pesticide products.

Pesticide contamination of working areas should be cleaned up as soon as possible. Allowing accumulations increases the risk of worker exposure. In the manufacture of Kepone, 76 production employees out of a work force of 113 experienced effects of pesticide exposure due mainly to gross contamination of the workplace. Kepone covered most of the plant equipment and work surfaces, in some places (notably in packaging operations) to a depth of 2 feet [84]. The method of cleaning is as important as the frequency to prevent worker exposures. Proper

personal protective equipment must be worn by workers during cleaning. A pesticide formulating worker was cleaning plant apparatus after removing his protective equipment and was overexposed to parathion [320].

Disposal of pesticide wastes also can cause exposures. A pesticide manufacturing worker sustained organophosphate poisoning while dumping waste [74]. The disposal of spills and toxic wastes into the general sewage system can create problems due to the mixing of materials such as acids, caustics, phosphorus, arsenic, and cyanide compounds which may interact to release toxic gases into the workplace. The disastrous results, including contamination of fisheries and recreation areas and subsequent multimillion dollar lawsuits, that arose from spillage of Kepone into the James River demonstrate other problems that such dumping can create [84].

EPA has established regulations defining prohibited procedures pertinent to the disposal of surplus containers and pesticides (Federal Register 39:36867, October 15, 1974). Specifically, open dumping is prohibited as is open burning, except for small quantities of combustible containers not exceeding 50 pounds or the quantity emptied in a single workday, whichever is less. Water dumping is generally prohibited. Local, state, and Federal regulations should be consulted whenever disposal occurs. Among the suggested precautions are incineration and burial in a manner not detrimental to the air or water environments.

(b) Personal Hygiene and Sanitation

Habits of personal cleanliness can play a significant role in protecting pesticide workers from exposure. Each worker must keep not only his body, but also any object which comes into contact with his body, free from pesticide contamination. The hands should be washed before eating or smoking so that materials entering the mouth do not carry pesticides into the body by ingestion or by inhalation. It is especially important to wash the hands before going to the toilet. Hands soiled with parathion absorbed the pesticide at only a 12% rate, compared with the scrotum which absorbed the pesticide at a 100% rate [20].

Washing methods and facilities must be planned to avoid recontamination or exposure. Faucets for handwashing should be operable by a device, such as a foot treadle, that does not require hand contact. Soap should be dispensed on a per use basis, rather than in a reusable bar form. Abrasive materials which remove layers of skin, or strong alkalies or solvents which defat the skin, should not be used. Individual-use towels should be provided for drying the hands. Even with a carefully selected cleaning material, frequent washing tends to make skin more vulnerable to penetration by pesticides. For that reason, a cream to counteract defatting of the skin should be available. Mirrors should be located over washbasins to facilitate washing the face and neck. The face can absorb parathion, for example, at three times the rate of the hands [20]. A study of body surface exposures to carbaryl among formulation workers showed that the face and neck receive an exposure at least as great as

that of the hands [18].

Showering can be somewhat effective in removing pesticide residues from the body surface. Sansone et al [307] conducted a simulation study to assess the effectiveness of various work practices in controlling exposure in materials handling operations. Showering with soap and water removed a substantial amount of skin contamination, leaving some residue on the face. Residues in the towels indicated some removal during toweling of the body. To accommodate worker showering, pesticide plants should be equipped with locker and shower rooms laid out so that workers exit from dirty to clean areas. Workers at Life Science Products failed to shower at the end of the workshift, aggravating their exposure to Kepone and other materials. Their shower facilities were uncomfortable to use, so the workers avoided showering there after work, and 76 of the 113 workers contracted dermatitis [84]. Showers should be located in a sheltered area with a disrobing room on one side for removing contaminated work clothing and with a separate, clean dressing room on the other side so that clean workers do not recontaminate themselves or their street clothing.

Materials that contact the body should be kept as scrupulously clean as the body itself. This practice is best performed by keeping all materials and activities involving eating, drinking, or smoking out of pesticide handling areas. Both lunchroom and smoking areas should be separated--located in another building, if possible--from pesticide manufacturing and formulating operations. OSHA has cited at least one pesticide

manufacturer for allowing employees to eat in a pesticide production area. Cigarettes and other forms of tobacco, food, cough drops, chewing gum, or drink should not be carried by workers to their job locations. Clean areas to store such materials away from pesticide production should be available. Food and beverage utensils or containers should never be used in pesticide handling. This practice was not followed by a company which allowed a packing shed to be used as a rest/break area. An employee who mistook aldicarb granules in the shed for coffee creamer was poisoned by his contaminated coffee [74].

Emergency Procedures

Sudden, unexpected calamities within pesticide manufacturing and formulating operations can greatly increase exposure risks. When fires, explosions, collisions and other accidents, or natural forces such as floods, storms, and earthquakes, damage pesticide equipment or containers, the two immediate problems are protecting workers from exposure and treating workers who have been exposed. These problems are usually aggravated in emergencies because of the gross amounts of pesticide that can escape and the limited amount of time in which to deal with them.

In a fire that occurred in a pesticide packaging plant in Tulare County, California [305], firemen and local residents were threatened with pesticide exposure. The fire destroyed containers, releasing large quantities of pesticide chemicals.

Another incident involved the wreck of a tank truck

containing 1,3-dichloropropene. The spilled liquid released large amounts of vapor which overexposed 11 firemen on the scene [74].

The importance of time was demonstrated in one fatality due to pesticide poisoning. After accidental ingestion of an unknown liquid formulation, no antidote could be administered because the pesticide was not immediately identifiable [329]. Blood ChE tests were normal, so acetylcholinesterase (AChE) inhibition was not suspected as the mechanism of intoxication. However, it was later determined that the chemical was a carbamate insecticide which depresses AChE activity, and which has a reversible effect on blood ChE. A more timely indentification of the pesticide would have indicated the proper treatment and possibly prevented this death.

Many times, lack of prompt action or incorrect treatment will increase the seriousness of an exposure. In OP poisonings, the errors most often made have included: failure to recognize the potential seriousness of a poisoning and consequent failure to keep the victim under close observation for at least 24 hours, failure to identify accurately the chemical to which the patient was exposed, failure to decontaminate the victim's skin adequately, failure to give adequate amounts of atropine and/or pralidoxime chloride (2-PAM) when indicated, and failure to carry out a confirming blood ChE determination [329].

In any emergency situation, a warning system is necessary to inform employees of hazardous work conditions. Warning systems include fire alarms, devices to detect excessive airborne

contamination, devices on equipment to warn of hazardous temperature and pressure extremes, and alarms to warn employees of dangerous spills. Each employee should be trained to recognize alarms and to know what to do when a warning is sounded.

Protective equipment for use in escaping from hazardous areas should be located inside areas where emergencies may occur and should be convenient to employees who may have to use it. Escape equipment should include a respirator, ideally with full-face protection. The respirator must provide workers with adequate oxygen so they will not lose consciousness or breathe hazardous fumes before they can get out of the area. Face protection is necessary to avoid eye irritation, so workers can see to get out of the area. Escape equipment is intended for escape use only; it is not adequate for extended protection or rescue work. Only designated workers should be allowed to remain in or to reenter hazardous areas for purposes of shutting dowr equipment, for containing or cleaning up spills or, most importantly, for rescuing workers who may still be inside. For these situations, rescue equipment should be available that provides more complete protection than escape equipment. Full body covering and air-supplied respiratory protective devices should be used. Protective body covering must be carefully selected. A firefighter was overexposed to methyl bromide even though he wore a respirator and complete protective clothing. The fumigant was able to penetrate the asbestos fabric in his protective suit [74]. In another incident, the need for a

self-contained breathing apparatus was demonstrated in an incident of fire involving methomyl. Heat from the fire caused large amounts of the toxic carbamate pesticide to vaporize. Firemen not wearing the apparatus were poisoned [74].

As mentioned earlier, many dermal and eye exposures can occur in pesticide manufacture and formulation. Because of this, showers and eyewashes are necessary in areas where these exposures might occur. Emergency facilities should be conveniently located so that they may be quickly and easily reached. Pathways to eyewashes should be kept clear of any hazards or obstructions to a blinded worker. For example, a pair of rubber gloves were observed lying in an eyewash fountain during a NIOSH site visit [8(p 92)]. These facilities also need to be checked frequently to make sure that pipes are not frozen or clogged and that there is no pesticide contamination which could worsen exposure.

There should be at least one person trained in first aid present during each shift. This person can take care of injured employees until help arrives or until the employee can be taken to a doctor. Only trained personnel should use resuscitation equipment or give antidotes.

Although fires, explosions, leaks, and spills are the most frequent types of emergency situations, other types of emergencies are possible. Earthquakes are a very real danger in California. One company's safety manual [330] gives specific instructions on what to do in the event of an earthquake. Power failures could be dangerous if they cause equipment to shut down

suddenly. Also, the possibility of a natural disaster such as a tornado, hurricane, or flood may exist. Companies should consider the various risks associated with their geographic area and climate, and plan for emergencies accordingly.

Maintenance

Equipment failures in pesticide manufacturing or formulating plants frequently cause pesticide emissions. If employees are in the vicinity of the equipment when it fails or if they must enter the contaminated area to repair the faulty equipment, the emissions can result in exposures. During 1975, California reported that pesticide exposures due to equipment failure were second only to exposures caused during the transfer of materials [29]. The number of occurrences of this type of exposure can be reduced by decreasing the number of equipment failures through an effective inspection and maintenance program [29].

The importance of inspection in pesticide manufacturing and formulating plants is typified by the following example. An employee was exposed to mevinphos when it spilled on his face and eyes from a rusted can which had developed a leak. The author noted that if the company and the employee had kept a careful watch on the condition of the containers this incident might not have occurred [29]. Several pesticide manufacturers and formulators have recognized the importance of this by including inspection procedures in their operations or safety manuals [331].

The inspection of process equipment and control equipment such as ventilation systems can be very important. In plants where total containment is used as an engineering control so that employees need not habitually wear personal protective equipment, the failure of process equipment or the ventilation system can seriously increase the probable occurrence of exposures. Frequently, equipment which is near failure or is in disrepair will not perform its function in the normal manner. Regular inspections can detect abnormal conditions so that maintenance can then be performed.

Carefully kept records of inspections and maintenance (both preventive and regular) can assist plant management in two ways. Records of equipment installation, maintenance, and failure can assist plant management in setting up inspection and preventive maintenance schedules. If equipment is inspected, replaced, or repaired before failure is likely, the risk of exposures occurring can be reduced. The company can benefit from a schedule of preventive maintenance through reduced downtime. Preventive maintenance can be scheduled for many pieces of equipment at one time. Records of equipment failure can be used by plant management to make decisions about which types or brands of equipment operate safely for the longest time.

Operating or safety manuals of pesticide manufacturing and formulating companies often contain procedures for performing maintenance [331], including procedures for precleaning, "lock out," and the "buddy" system. Numerous examples where proper procedures were not followed and resulted in exposures are

reported in the literature [29,113,297].

Maddy and Topper [29] suggested that mechanical cleaning be used whenever possible before maintenance work is performed on equipment that is contaminated with a pesticide chemical. Several of the exposure incidents described in his report could have been prevented if this practice were followed. However, the maintenance workers should be warned that even though the equipment is precleaned it may still be contaminated. Maintenance workers should be trained to recognize potential exposures because they have to work in many areas where the probability of exposure is high.

"Lock out" procedures can vary from plant to plant because of differences in equipment. However, some points are applicable to all "lock out" procedures, including power shutoff, material flow shutoff, and the wearing of the proper personal protective equipment for the maintenance operation being performed. Power shutoff generally includes relief of internal pressure as well as electrical and mechanical power shutoff. Maintenance safety manuals generally include procedures for locking the power off and posting signs to indicate that power should not be turned back on until the maintenance is completed. Material flow shutoff is similar to power shutoff. Procedures should include locking valves in a closed position, installing blinds (plugs) in the pipe, or removing a section of pipe to prevent pesticides from entering equipment. When precleaning procedures cannot be used, personal protective equipment must be worn when performing maintenance tasks to prevent exposures from occurring. The

required equipment should be specified in the operations or safety manual.

When performing maintenance that requires a worker to enter a piece of equipment, the buddy and permit systems will help protect the worker from accidental exposure. The buddy system requires that a second employee be in visual and voice contact with the employee who entered the piece of equipment under repair. This contact is maintained throughout the maintenance process. The employees are also usually connected by a lifeline so that the employee who is inside the equipment can be pulled out if he is injured or poisoned. The permit system requires that the worker obtain a permit from a supervisor who, in turn, is responsible for ensuring that certain precautions have been taken before the permit is issued.

Support of Work Practices

Recommended work practices for materials handling procedures, housekeeping, personal hygiene, tank entry procedures, and use of personal protective equipment can successfully prevent worker exposure to pesticidal chemicals only if accepted and continuously observed by the worker. Employers can encourage worker acceptance of work practice controls by informing workers about the risks associated with their occupations and by supporting the work practice controls through proper supervision and utilization of administrative controls.

(a) Posting and Labeling

Recognition of danger is a significant factor in the

prevention of injury or illness [29]. One of the findings of the NIOSH National Occupational Hazard Survey (NOHS) is that most workers are unaware of the hazards of their jobs [332]. The survey cites the widespread use of trade name products and the lack of a uniform labeling system as reasons why it is difficult for workers to know the chemical hazards to which they are exposed. Obviously, treatment of a poison victim is very difficult unless the chemical composition of the poison is known.

Blodgett and Musgrove [84], in summarizing hearings on Kepone contamination, stated that an epidemiologist who surveyed the Kepone facilities found no informational signs or posters to indicate that Kepone was hazardous.

Information about hazards, even though covered in a training program, should be available in the workplace as a reminder and reference for trained workers, and as a warning to others who may inadvertently enter a hazardous area. Labels should be applied to process equipment, and signs should be posted at points of access to hazardous operations.

EPA enforces requirements for labeling that are authorized under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and under the Federal Environmental Pesticide Control Act (FEPCA). These laws require labeling of all containers of pesticides that are commercially sold. Product labels must contain the common and chemical names, signal words if required, such as danger, warning, and caution, and first-aid procedures in case of an accident. EPA does not require that labels be affixed to process equipment or to containers other than those in which

pesticides are distributed for sale. In addition, the labels required by EPA do not include information concerning safe work practices and use of protective equipment. Product label requirements are based on toxicity of the final product. Some active ingredients, in concentrated form, may be more toxic than the label indicates. Thus, there are several situations in the workplace where product labels do not provide sufficient information to assure protection from overexposure.

In a pesticide manufacturing or formulating plant, anything that contains a pesticidal chemical--including drums, bags, and processing equipment--should be labeled to indicate contents and hazards. Signs should be posted to aid workers in determining what type of respirator and other protective equipment to use. Signs should also indicate what to do in the event of an emergency or spill. Some of the labeling practices observed during site visits [8(pp 58,98)] to pesticide plants include content and hazard labels on product containers, content and pressure labels on reaction vessels to prevent premature opening of a pressurized tank, color-coded pipes, and directional flow labels on pipes. Other signs observed on site visits [8(pp 5,38,91)] include "No Smoking" signs and reminders to wash hands and observe other personal hygiene requirements.

Posting various safety and health warnings in conspicuous areas within the plant informs workers of hazardous operations. Posters or signs should be used to warn workers about protective equipment required for entry to and limited access of restricted areas, to identify emergency equipment and exits, and to specify

procedures for operations such as maintenance or repair of process equipment. When maintenance is in progress and the potential for exposure increases, signs should be posted to inform workers that such operations are taking place.

Generally, labels and signs support other recommended work practices by identifying areas where those practices are required and by warning of specific hazards associated with pesticide products.

(b) Training

The recognition of danger is especially difficult when there are no immediate acute effects. Without special training regarding the chronic effects of workplace chemicals, the methods to avcid exposure, and the symptoms of exposure, workers may become chronically overexposed to pesticidal chemicals. The following cases demonstrate instances in which workers' lack of awareness of toxic effects of the chemicals they handled contributed to their overexposure.

Hine [112] reported that 9 of 10 workers overexposed to methyl bromide were not informed of the hazard of that fumigant. Four of these overexposures resulted in fatalities. In an incident reported by Vale and Scott [37], a woman suffered severe poisoning and neurologic damage while employed in a plant formulating a preparation of demeton-S-methyl, an OP insecticide. The woman was never told in any detail of the possible effects of exposure to the products with which she was working. She had, for example, never realized that the abdominal cramps she had occasionally experienced were probably due to the

demeton-S-methyl exposure, or that pinpoint pupils were another sign of exposure.

Training is an important component of any program to reduce worker exposure to hazardous chemicals or physical agents. The Occupational Safety and Health Act requires employers to provide their employees with training that will enable them to understand the nature of hazards to which they are exposed and effective methods to protect themselves. Training for supervisors should also include detailed information on emergency procedures. A National Research Council (NRC) study [333] on informing workers about cancer and other occupational illnesses suggested that workers be given a broad understanding of the hazards associated with their occupation. The study recommended that training include substance identification, location in the workplace, routes of exposure, measures to reduce exposure, signs and symptoms of overexposure and health consequences (even when extrapolated from animal data), proper use and maintenance of personal protective equipment, emergency procedures, and first aid. The last three items are particularly important.

Personal protective equipment is not effective if used improperly. A worker using an air-purifying respirator in an environment where the concentration of the contaminant exceeds the capacity of the respirator's filtering medium is not protected from overexposure. Similarly, a worker wearing a respirator that fits poorly is not adequately protected. Failure to wear personal protective equipment in areas where exposure is possible is a frequent occurrence when workers do not fully

understand the serious nature of the hazard involved.

The training program should describe the role of each work practice in reducing potential exposure. The need for and value of each work practice should be clearly understood by the worker. The employee who is able to recognize the hazard and knows the means to control it is better equipped to protect himself from exposure. If the employee recognizes symptoms of exposure, he or she can request medical attention sooner. Detection of the odor of a pesticide being handled while wearing a respirator should be recognized by the worker as a warning that the respirator is not functioning properly.

In summary, the training requirements are intended to reinforce the other work practices by enabling the worker to understand the nature of the hazards associated with pesticidal chemicals and how to avoid overexposure. Worker acceptance of recommended work practices as well as an understanding of and the ability to avoid chronic health hazards can be improved through training.

(c) Supervision

Inadequate supervision was described as a cause of overexposure in a case in which a man was mixing 2,4-dichloro-6-(o-chloroanilino)-s-triazine in a tank when he began to notice itching and burning of his face and hands. A physician gave him local and systemic steroids for treatment of his rash. He had been provided with protective clothing but might not have used it at all times. In addition, some of the containers were not labeled to require the use of protective

equipment [297].

An employee cleaning a pump used in mevinphos production at a formulation plant was overexposed as the result of not wearing recommended safety equipment. He reported to a physician with symptoms that included miosis, excessive salivation, and excessive perspiration. He was hospitalized. His employer was issued a notice of violation for lack of adequate supervision of employees [297].

Inadequate supervision was indicated as a causal factor in some of the accidental overexposures to pesticides discussed earlier. The relationship between supervision and the implementation of good work practices is evident in most industrial situations. The potential is always present for production requirements to conflict with work procedures designed to prevent injury or illness. To protect workers' health in a pesticide plant, it is essential for supervisory personnel to be cognizant of the potential risks that occur to workers when proper work practices are not followed. Supervisors should be present to assure that proper procedures are followed during start-up, loading and unloading, and during tank entry operations. Supervisors should also be prepared to direct other workers during emergency situations. Occasional checks should be made to be certain that personal protective equipment and protective clothing are properly worn. Supervisors should also know and watch for signs of overexposure to pesticides and should recommend medical attention for workers who exhibit signs of overexposure. One positive strategy for concerned management

would be to rate supervisory personnel on understanding and implementing safe and healthful work practices in addition to normal factors such as productivity and economy of operation.

(d) Administrative Controls

Administrative controls are actions taken by the employer to schedule operations and work assignments in a way that minimizes the extent, severity, and variety of potential exposure. For example, only necessary personnel should be permitted to work in areas where there is a high risk of exposure. The duration of exposure may also be reduced by rotating employees between assignments that involve exposure and those that do not. Minimizing the number of different pesticides that an individual worker is exposed to is also desirable. This practice would make it easier to monitor effects and, more importantly, would avoid possible synergistic effects that may result when exposure to several different chemicals occurs.

There are four activities that can support work practices: labeling and posting, training, supervision, and administrative contols. The emphasis in training should be on developing good work practices to prevent emergencies, accidents, injuries, and overexposures. The educational process should be reinforced through labeling and posting that identifies hazards and repeats information concerning proper procedures. Labels and signs alsc serve as warnings to uninformed individuals in the plant. Supervision is an essential element in the proper implementation of good work practices as well as a resource for dealing with emergency situations or for observing signs of overexposure in

workers. Finally, administrative control is an additional method of minimizing worker exposure through allocation of work assignments and in conjunction with other recommended work practices.

VI. DEVELOPMENT OF THE STANDARD

Need for the Standard

The use of pesticides is based on their ability to interfere with basic biochemical processes of living cells and thereby kill the cells or leave them metabolically altered. Numerous examples of adverse effects of all classes of pesticides on individual humans, on worker populations, and on animal test systems are detailed in Chapter III. Pesticides have caused diverse toxic effects on various human organs, including the skin, kidneys, eyes, lungs, and reproductive system. Certain pesticides including inorganic arsenic compounds, certain hexavalent chromium compounds, acrylonitrile, amitrole, benzene, and creosote are probable occupational carcinogens based on data derived from human epidemiologic studies and animal tests. In addition, other pesticides are suspected occupational carcinogens, based on data derived from animal experiments. Various pesticides have produced significant teratogenic, neurotoxic, or reproductive effects in animal test systems.

Each year in the United States, occupational exposure to pesticides is directly responsible for many illnesses and injuries. In California alone, during 1975 and 1976, there were 96 reported cases of occupational illnesses resulting from exposure to pesticides in manufacturing and formulating plants [29,297]. Of these, 63 were systemic, 14 involved skin injuries,

17 involved eye injuries, and 2 involved both the skin and the eyes. The cases were the result of exposure to a wide variety of pesticides including mevinphos, captan, diazinon, methomyl, ethylene dibromide, sulfur, methyl bromide, and chlorothalonil.

NIOSH site visits to pesticide manufacturing and formulating plants indicated the need for better control. For example, many plants lacked the capability for medical or industrial hygiene surveillance; employees were often ignorant of the hazards present in their workplace. Skin and respiratory exposures to pesticides, such as prometon during formulation [8(p 14)] and arsenic compounds during production, were observed [8(p 90)]. In addition, the two recent incidents of severe neurotoxic effects in workers exposed to Kepone and leptophos and of reproductive disorders in workers exposed to DBCP emphasize the potential danger to all workers engaged in the manufacture and formulation of pesticides.

Relationship to Other Standards

Authority to regulate hazards arising from the manufacture, formulation, distribution, and use of pesticides resides with several Federal agencies and the states. The Occupational Safety and Health Administration (OSHA) has authority for regulating employee exposures arising from pesticides and other chemicals in manufacturing and formulating plants. States are generally responsible for regulating the occupational health of farm workers and applicators within the framework of EPA programs.

Responsibility for administration of the Federal

Insecticide, Fungicide, and Rodenticide Act (FIFRA) was transferred to EPA in 1970. FIFRA requires the labeling and registration of pesticides in interstate commerce and the establishment of tolerances for pesticide residues in food products. The Federal Environmental Pesticide Control Act (FEPCA) of 1972 extended the requirements of FIFRA to all pesticides, including those formulated and sold within a single state, and contains requirements for establishing a program to certify pesticide applicators for certain restricted pesticides. Pursuant to FEPCA, EPA has established a pesticide reregistration program which includes a rebuttable presumption against registration (RPAR) process. If data, including carcinogenicity, teratogenicity, reproductive effects, ecologic effects, etc, indicate that a pesticide may be harmful to man or the environment, the Administrator of EPA presumes that the pesticide causes certain effects, and the manufacturer has opportunity to rebut that presumption.

Other Federal agencies having responsibilities with respect to pesticides include the Department of Transportation (DOT), the Federal Trade Commission (FTC), the Food and Drug Administration (FDA), and the Federal Aviation Administration (FAA). DOT, under requirements of the Hazardous Materials Transportation Act, imposes labeling and transportation restrictions on pesticides that are "Class A and B Poisons" (see Table XIV-17). The Federal Aviation Act specifies controls in aerial applications of pesticides. Under this Act, FAA requires certification of aircraft operators before they are permitted to spray. FTC has

proposed a regulation to prohibit pesticide advertisements that claim the product is safer than the label indicates. FDA enforces food tolerances set by the EPA. In summary, the regulatory jurisdictions of agencies other than OSHA include pesticide labeling, registration, setting and enforcing tolerances in food products, certification and control of exposure of applicators, setting field reentry standards for farmworkers, transportation, and advertising.

Under the Occupational Safety and Health Act of 1970, states may elect to have their own occupational safety and health programs for regulation, provided they meet Federal approval. California has rather comprehensive standards covering pesticide application, including specific rules for fumigation. Medical surveillance, including ChE testing, is required for mixers, formulators, loaders, ground and aerial applicators, and flaggers in the agricultural use of pesticides. California also requires physicians who treat cases of occupational illness or injury to report the cases to the state, which may then investigate the cases in greater detail. However, the state's regulations which relate to workers in pesticide manufacturing and formulating plants are similar to those in 29 CFR 1910 as enforced by OSHA.

OSHA has promulgated general requirements that apply to all industries and occupational exposure limits that apply to certain pesticides (see Appendix III). The general standards cover industry in general and are not directed specifically towards pesticide production. Practices such as use of personal protective equipment, sanitation, and fire protection are

contained in the general standards. Exposure limits, developed by the American Conference of Governmental Industrial Hygienists (ACGIH), in terms of 8-hour time-weighted average airborne concentrations, were adopted by OSHA in 1970 for a number of pesticide active ingredients (see Appendix III). OSHA has also developed regulations for two chemicals having minor use as pesticides: benzene and beta propiolactone. NIOSH has developed various criteria documents and recommended standards for limiting exposure to materials registered as pesticides (see Appendix IV). These documents include recommended medical surveillance, work practices, and other elements of a total occupational health standard for protecting workers.

Form of the Standard

The need for effective protection of workers from hazardous exposures in the manufacturing and formulating of pesticides requires a comprehensive standard. A large number of chemical substances may cause exposure in a variety of operations.

For a single chemical substance, a standard which sets a limit on worker exposure in terms of time and concentration in the workplace air is useful. Such a standard would be particularly appropriate when exposure to the substance through inhalation is the most significant hazard. However, a workplace air concentration limit is useful only if the methods and frequency of monitoring can be specified. The method by which protection from airborne concentrations is achieved must also be part of such a standard and should reflect a preference for

engineering controls over respirator use.

The derivation of environmental (workplace air) limits for over 1,500 pesticide active ingredients and various inerts, additives, intermediates, and solvents in pesticide manufacturing and formulating cannot be accomplished as quickly or effectively as the design of good work practices and effective engineering controls. The number of materials to be sampled and the complexities of sampling and analysis in monitoring all the pesticides present would be an almost insurmountable task for many formulators. Exposure to nonairborne pesticides as a result of splashes, spills, deposits, and handling is not considered in the establishment of an environmental limit. For many pesticides discussed in Chapter III, particularly the organophosphosphorus (OP) compounds, there are significant systemic effects arising from exposure by absorption through skin and other body surfaces, and there are local effects from contact of the chemical with skin, mucous membranes, eyes and their surrounding structures. Some pesticides, such as dibromochloropropane (DBCP), apparently induce effects at such a low dose that the threshold of effect is at or near the threshold of detection by a reliable analytical technique.

For the production processes used in manufacturing and formulating pesticides, properly engineered equipment provides the best control. The processes are predictable, and controls can be planned and installed to keep pesticides in known limited locations. The costs and effectiveness of engineering controls are predictable and lend themselves to technical evaluation. The

major drawbacks to engineering controls are that they may limit access to processes for observation and control; they require maintenance; and they require a length of time for installation. Engineering controls are desirable as part of a pesticide standard, although variations in processing equipment preclude the development of any standard that specifies the use of particular hardware or systems.

When leaks, spills, or emergencies cause the release of pesticides into worker-occupied areas, work practices must be relied upon for protection. Work practice controls are necessary, especially to complement engineering controls in situations where the latter give incomplete protection from exposure. Work practice measures also minimize exposure during the cleaning and maintenance of engineering control equipment. They are flexible and can be initiated in a relatively short time period. The chief weakness of work practices is their reliance on informing and motivating employees to protect themselves. The variety of toxic materials handled makes it advantageous to teach general work habits that will protect employees without regard to the types of pesticides they handle. However, the training of employees, as well as all other work practices, should be attuned to the risks present. As discussed in Chapter III, pesticides may affect the body through a variety of exposure routes and cause many different types of effects by a wide range of doses. Because of their diverse toxic actions, pesticides are subjected to different levels of control. Multiple levels of control are designed to allow pesticide manufacturers and formulators to

expend resources on controlling those pesticides that present the greatest risk of adverse toxic effects. The most toxic pesticides require stringent engineering and work practice controls. For those pesticides classified as less toxic, such strict control may be unnecessary.

Basis for the Recommended Standard

(a) Development of a Classification Scheme

One of the earliest toxicity classifications was developed by Hcdge and Sterner [334], who used the oral LD50 of the substance as the numeric criterion for classification. This approach was modified by Gleason and Hodge [335], who established six toxic categories on the basis of oral LD50 values and assigned designations to these categories. Pesticides with an LD50 less than 5 mg/kg were labeled "super toxic," while those with an LD50 greater than 15,000 mg/kg were labeled "practically nontoxic" (see Table XIV-15). This system is most commonly used to describe the toxicity of a substance and was first employed to guide physicians in the treatment of victims of accidental poisoning by ingestion.

With the passage of FIFRA in 1947, toxicologic classification schemes assumed a new significance. The classification scheme was used to determine the warning words and precautionary statement for the product label.

Until 1970, the US Department of Agriculture (USDA) had the responsibility for administering FIFRA, and set up a toxicity classification scheme to be used in the designation of pesticides

regarded as "highly toxic to man." Pesticides so designated were required to bear the word "Danger" along with the word "Poison" and a skull and crossbones on their labels.

The toxicity classification scheme developed by USDA emphasized the importance of inhalation and dermal exposures in addition to oral intakes and set forth criteria for all three routes of exposure.

In December 1970, EPA was formed and given jurisdiction over FIFRA. FIFRA was significantly extended in October 1972 by FEPCA. FEPCA introduced the concept of "restricted use" and "general use" pesticides. Pesticides classified as "restricted" were to be made available only to individuals who were certified as competent in their use, while no such restrictions were placed on users of pesticides classified as "general." In July 1975, EPA promulgated final regulations (40 CFR 162) implementing registration procedures. A classification scheme with four toxicity categories was introduced to control labeling, warning, and precautionary statement requirements. This classification scheme was based on oral, inhalational, and dermal toxicity (see Table XIV-16).

Pesticides that are intended for household or other domestic application are classified as "restricted" if they are in toxicity Categories I or II. In making classification decisions, EPA also takes into account whether the pesticide causes any subchronic, chronic, or delayed toxic effects in man under normal conditions of use. A pesticide that causes more than "minor" effects is classified as "restricted."

DOT developed a classification scheme for chemical substances to effect their safe handling during shipment and transportation. The scheme consisted of the dosage criteria below which pesticides were presumed to be toxic to man (see Table XIV-17). Gaseous substances that meet any of the criteria are designated as "Class A Poisons"; solid and liquid substances meeting the criteria are designated as "Class B Poisons." All such substances must be labeled and handled with special precautions during their shipment.

Some nations and international organizations have also developed classification schemes. At a World Health Organization (WHO) conference in 1971, a set of criteria based on rat oral LD50 values was proposed for labeling of pesticide formulations (Table XIV-18). WHO reported that authorities in a number of European countries have adopted these rules and found them both "workable and consistent" [336].

In 1975, WHO recommended a scheme to classify pesticides in order to distinguish between the more and the less hazardous forms of each pesticide [337]. An added feature of this classification method was the inclusion of the physical state of the substance in the criteria. The classification criteria included only dermal and oral exposures. However, the WHO report did point out that if the criteria are applied to solvent-based pesticide formulations, account must be taken of volatility and consequent inhalation toxicity (see Table XIV-19).

Ulanova [338] reported a system of classification of substances according to the level of toxicity that has been

adopted by official agencies of the USSR. The system includes four different class levels, based on toxicity by oral, inhalational, and dermal routes (see Tables XIV-20). Kaloyanova [339] reported a Bulgarian classification scheme, which is similar to the Russian in format, but whose values vary (see Table XIV-21).

Classification schemes based on chronic effects of pesticides are not presently in wide use. OSHA has proposed a system for classifying toxic substances according to evidence of carcinogenicity. The four-category system includes specific types of tests which serve as a basis for classification (Federal Register 42:54148, October 4, 1977).

While there are some differences among the aforementioned systems for classifying pesticides in terms of their acute toxicities, the systems are quite similar, with respect to the oral, inhalational, or dermal toxicity range for very toxic or highly toxic substances.

NIOSH recommends three toxicity categories for the various routes of exposure for defining the hazards of pesticides (see Table VI-1). The recommended classification criteria are very similar to those used by EPA for registration purposes. EPA Categories I and II and NIOSH Groups I and II are identical. NIOSH Group III encompasses both Categories III and IV in the EPA scheme. Listed in Appendix I are approximately 1,500 active ingredients grouped by toxicity. For each pesticide, the most concentrated registered product has been used to determine the resultant group classification because this form is most likely

to be present in manufacturing and formulating workplaces. Registered product data were provided by EPA. In certain cases, seemingly conflicting EPA data indicated that a particular active ingredient had been classified in more than one EPA toxicity class. In those cases, the compound has been grouped in the more stringently controlled NIOSH group. Furthermore, approximately 350 compounds were placed in NIOSH Group III because each does not appear as a single concentrated ingredient in any pesticide product. These compounds include certain substances that have uses as emulsifiers, detergents, solvents, and other nonpesticidal uses. However, they are registered active ingredients because they have biologic activity. It should be stated that there are biologically active emulsifiers, detergents, solvents, and other compounds used in the manufacture and formulation of pesticides that are not EPA-registered active ingredients and therefore do not appear in Appendix I.

TABLE VI-1

DEFINITIONS OF GROUPS I, II, AND III

Hazard Indicators	Toxicity Categories I	II	III
Irreversible Effects	Probable or Suspected carcinogenic, neurotoxic, mutagenetic, teratogenetic, or reproductive effects		
Oral LD50	< 50 mg/kg	50-500 mg/kg	> 500 mg/kg
Inhalation LC50	< 0.2 mg/l	0.2-2 mg/l	> 2 mg/l
Dermal LD50	<200 mg/kg	200-2,000 mg/kg	>2,000 mg/kg
Eye effects	Corrosive; corneal opacity not reversible within 7 d	Corneal opacity reversible within 7 d; irritation persisting for 7 d	No corneal opacity; irritation reversible within 7 d
Skin effects	Corrosive	Severe irritation at 72 hr	Moderate irritation at 72 hr

Pesticides implicated in Chapter III as probable occupational carcinogens or suspected occupational carcinogens, teratogens, neurotoxins, and toxins to the reproductive system are classified in Group I regardless of acute toxicity. The data on which these decisions are based are also presented in Chapter III. Various pesticides are currently in the EPA RPAR process, including amitraz, cadmium, diallate, endrin, maleic hydrazide, and pronamide due to suspected carcinogenicity; benomyl, maleic hydrazide, cadmium, and thiophonate-methyl due to suspected mutagenicity; benomyl, cadmium, and ethylene bisdithiocarbamates due tc suspected teratogenicity; and benomyl, ethylene dibromide (EDB), maleic hydrazide, hexachlorocylohexane, dimethoate, and lindane due to suspected reproductive effects. EPA's data for these pesticides have not been reviewed by NIOSH; however, once a decision is made concerning reregistration of these compounds, each should be classified in the recommended NIOSH scheme following further review of the EPA data.

Throughout the process leading to the development of this recommended standard, the major emphasis has been on providing protection for workers engaged in the manufacture and formulation of pesticides in the light of necessary time constraints. The recent serious episodes of occupational poisoning due to Kepone and leptophos indicate that effective controls need to be implemented immediately, not several years hence. The relatively long period of time and tremendous expense that would be required for the development of individual recommended standards for all

pesticides mandate that a different approach be taken. A generic or industry-wide approach to the development of a recommended standard for the manufacturing and formulating segments of the pesticide industry, based primarily on effective engineering controls, work practices, and personal sanitation practices, was felt to be the best strategy. Several classification systems that NIOSH was able to find have been examined, and only after their evaluation, was the decision made to adopt a scheme compatible with that used by EPA. Standardization was not the main objective, but it is obvious that there is a definite correlation in all classification schemes examined, especially in the areas of extreme or high toxicity. The various systems for classification do not differ significantly in terms of their scientific merit. The EPA system is the only other pesticide toxicity rating scheme officially used by the US Government and, since it is in general agreement with those standards recommended by recognized agencies, to devise a different method of classification would result in unnecessary complication. The burden on both government and industry will be lessened through the use of uniform criteria.

The basic toxicologic parameter of the recommended classification scheme is the acute lethal dose or concentration. As with any other statistically derived value, variability can be expected in its determination. The variability may be introduced with the number of test animals used, with differences in diet and/or environmental conditions, and with any of a number of factors that affect experimental results. Accordingly, it is

understood that there will be chemicals that seem to bridge two toxicity groupings. Consequently, such pesticides are placed in the group that is more stringently controlled. NIOSH recognizes the resultant effect on the classification and regulation of certain pesticides. However, this theoretical disadvantage is more than offset by the facility with which pesticides can be classified under the proposed scheme.

(b) Medical Surveillance

Preplacement medical examinations should be made available to employees prior to any occupational exposure to pesticides. The purposes of such examinations are the identification of any conditions or disorders predisposing employees to pesticide toxic effects and the assessment of employee ability to use respiratory protective devices. Certain employees should also be counseled by a physician before occupational exposure in those cases where the employees' state of health or parental status poses a peculiar risk to themselves or their children.

Exposure to pesticides has caused a variety of local and systemic health effects. Local effects include chloracne [134,135], erythema [144,145] and other dermal reactions [139-141], and various injuries to the eyes [143]. Organ systems affected by pesticide exposures are the nervous [37,55], reproductive [118,119], hepatic [121,124], renal [128,129], hematopoietic [152,154], cardiovascular [161], and respiratory systems [125, 148]. There is also evidence that some pesticides induce cancer in various organs [48,59,167]. Therefore, annual physical examinations are also recommended.

OP pesticides may affect the nervous system by inhibition of cholinesterase (ChE) activity. This effect is usually reversible by antidotal treatment; however, it is slowly reversible if not treated, and a series of low chronic exposures can lead to significant ChE depression. NIOSH recommends periodic determination of red blood cell (RBC) ChE for all workers exposed to OP insecticides. The frequency of such determinations should be based on the pesticide(s) to which an employee is exposed, his potential exposure levels, and his state of health. Frequency should be decided by the physician only after he weighs all of these factors and considers the results of previous determinations. RBC ChE may be determined as frequently as daily for certain special circumstances, but no less frequently than six times per year which is necessary in order to ensure that changes in the employee's workplace or working habits have not increased his pesticide exposure to unhealthful levels.

(c) Labeling and Posting

Employees should be apprised of pesticide hazards and methods to protect themselves. Although all employees who will be occupationally exposed to pesticides should already receive such information as part of their training, labels and signs serve as an important reminder. Labels and signs also provide an initial warning to other employees who normally may not deal with pesticides.

(d) Personal Protective Clothing and Equipment

Protective clothing and equipment protect the pesticide worker from exposure. In pesticide manufacturing and

formulating, employees should cover their body surfaces in order to avoid the local effects of contact with toxic chemicals and also to prevent systemic effects which may arise after absorption of pesticides through body surfaces.

Clothing and equipment should be carefully selected, used, and maintained to be effective. Studies have shown that many materials commonly used in protective equipment are not impermeable to pesticides and solvents [316,317]; however, materials selected for such clothing and equipment should be no more than minimally permeable to the substances involved in employee exposure. Employees must be thoroughly trained to properly use their personal protective clothing and equipment, especially respirators.

Maintenance of protective clothing and equipment includes inspecting, testing, cleaning, and reparing or replacing when necessary. The employer should arrange a system for storing and cleaning equipment and work clothing that guards against the contamination of street clothing or other personal effects of the employees.

(e) Informing Employees of Hazards

The toxic effects of pesticides and other chemicals involved in occupational exposure should be fully explained to employees, including probable and potential carcinogenic, teratogenic, mutagenic, neurotoxic, and reproductive effects. In cases where these effects are based on animal data, the risks to man should be explained. Employees should be taught to recognize symptoms of overexposure and to administer first-aid measures in

such cases.

Employee training should fully cover methods to protect workers from chemical exposures in routine work and in emergencies. Written information available to all employees should include toxicity data, first-aid measures, personal protective methods, emergency procedures, and applicable regulations for the substances to which they may be exposed. As plant processes change or new data come to light, employee training and available information should be updated.

(f) Work Practices

The manner in which employees perform their work should be directed to minimize their exposure. Handling pesticides in contact with skin surfaces should be avoided. Pesticides and other chemicals used in their manufacture and formulation should be kept in appropriate containers and processing equipment; leaks or spills should be promptly cleaned up. Disposal of pesticides and pesticide-contaminated materials should be performed by methods which limit exposure.

Employees should deactivate and decontaminate any equipment before maintenance, in order to prevent injury or exposure. Special precautions should be taken before entering enclosed spaces, especially to protect against respiratory exposure.

(g) Sanitation and Personal Hygiene

Employers should provide facilities to allow employees to wash off pesticides and other chemicals. Employees should be advised to cleanse themselves of pesticides to reduce skin exposure and contamination of food or tobacco products which

could lead to oral or respiratory exposure. For that reason, consumption of food, beverage, or tobacco products should be prohibited in areas where pesticides are handled. Sanitation and hygiene practices should be encouraged by employee training, supervision, and the posting of signs.

(h) Engineering Controls

To the greatest extent possible, pesticides and other toxic chemicals should be handled within closed systems to minimize employee exposure. Equipment should be designed and situated so that malfunctions do not cause release of chemicals into worker-occupied areas. Regular inspection and maintenance should be conducted to lessen the risk of leaks and malfunctions. Where there is likelihood of escaping pesticides, systems for recapture should be used, ie, exhaust ventilation for airborne pesticides and sumps for liquids.

(i) Monitoring and Recordkeeping

In order to detect, prevent, and treat employee exposure to pesticides, monitoring with concomitant recordkeeping should be periodically conducted. The effectiveness of engineering controls may be measured by monitoring the workplace atmosphere. The use and success of work practice controls can be assessed by observation of worker functions and by medical surveillance. Records of plant monitoring and employee medical examinations should be compared to detect any correlations between exposure and effect.

The Toxic Substances Control Act of 1976 requires that "Records of...adverse reactions to the health of employees shall

be retained for thirty years from the date such reactions were first reported to or known by the person maintaining such records...." Because medical examinations will often provide the first recognized evidence of an adverse reaction, whether at the time of the examination or retrospectively, it appears consonant with the Toxic Substances Control Act to require medical records on workers engaged in the manufacture or formulation of pesticides to be maintained for 30 years. Furthermore, records of environmental exposures should be kept for the same period, to allow correlation of a worker's exposure with his or her health.

VII. RESEARCH NEEDS

There is an obvious need for a wide range of toxicity testing for many of the 1,500 Federally registered pesticides. In a recent notice (Federal Register 41:7218-7375, February 17, 1976), FPA stated that it had reviewed the data in its files on approximately 650 of 1,500 registered active ingredients. Of those reviewed, approximately 470 required further testing before reregistration could begin. Types of tests required included long-term feeding, teratogenicity, mutagenicity, reproductive effects, oncogenicity, and various short-term tests. There is also a need for further studies to elucidate observed behavioral effects in animals and to relate them to humans.

The most important research needs stem from the need or desire for extra care when handling many pesticides. In the area of engineering controls, methods of controlling dusts, vapors, gases, or splashes and spills while performing operations such as packaging or transfer are clearly needed for both manufacturing and formulating. Although for certain operations controls do exist, improvements can be made. Improvement of engineering controls would have a positive impact on the health and safety of employees engaged in the manufacture and formulation of pesticides. Currently, the Control Technology Research Branch of NIOSH is undertaking a study with the purpose of documenting the types of engineering controls now being used in the manufacturing

and formulating industry. The results, to be published in 1979, will document the state of the art with regard to engineering controls and will elucidate those areas where the greatest research and development are needed.

A program should be undertaken to develop more effective and satisfactory personal protective clothing and equipment. Emphasis should be placed on developing cool, lightweight, and impervious clothing and equipment. The impermeability, or lack thereof, of various types of protective clothing or equipment, including aprons, gloves, gauntlets, and boots, is an extremely important factor in percutaneous absorbtion of pesticides. The permeability varies greatly, depending on the material and the chemical substance. The weave and finish of cloth also affect the permeability of clothing. The variations are so great that pesticide manufacturers and formulators should use only protective clothing and equipment that has been tested and found to be highly resistant to penetration of those chemicals of concern.

The decontamination of work clothing requires further research. Though some work has been done involving OC, OP, and carbamate insecticides, there is an obvious need for similar work on other pesticides, including substituted carbamate fungicides, halogenated fumigants, rodenticides, and most herbicides. In the studies done thus far, the results indicate that optimum conditions for decontamination can be estimated, but that in no case has decontamination been complete by the procedures examined.

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IX. APPENDIX I

CLASSIFICATION OF PESTICIDES

Group I

Acephate-met**
3-(alpha-Acetonylfurfuryl)-4-hydroxycoumarin
3-(alpha-Acetonylfurfuryl)-4-hydroxycoumarin, sodium salt of
Acrolein
Acrylonitrile (C)
Alachlor
Aldicarb*
Aldrin (C)(T)(N)
Alkyl amine acetate (48% C12, 18% C14, 10% C18, 9% C16, 8% C8, 7% C10) (as in fatty acids of coconut oil)
Alkyl amine hydrochloride (as in fatty acids of coconut oil)
Alkyl amine tetrachlorophenate (as in fatty acids of coconut oil)
1-(Alkyl amino)-3-aminopropane acetate (as in fatty acids of coconut oil)
1-(Alkyl amino)-3-aminopropane hydroxyacetate (as in fatty acids of coconut oil)
1-(Alkyl amino)-3-aminopropane propionate - copper acetate complex (as in fatty acids of coconut oil)
Alkyl amino betaine (46% C12, 24% C14, 10% C16, 8% C10, 7% C8, 5% C18)
2-Alkyl-1-(2-aminoethyl)-2-imidazoline acetate
Alkyl ammonium salts
Alkyl bis(2-hydroxyethyl) amine acetate (65% C18, 30% C16, 5% C14)
N'-Alkyl-N-(2-cyanoethyl)1,3-diaminopropane (as in fatty acids of coconut oil
Alkyl diamine monobenzoate (as in fatty acids of coconut oil)
Alkyl diethanolamide (70% C12, 30% C14)
N-Alkyl dihydroxyethyl amine oxide (50% C12, 22% C14, 10% C15, 8% C10, 5% C18)
N-Alkyl Dipropoxy-tert-amine (47% C12, 18% C14, 10% C18, 9% C10, 8% C16, 8% C8)
Alkyl (ethylcycloimidinium) 3-hydroxy-3-ethyl sodium alcoholate, 2-methyl sodium carboxylate-tridecyl polyoxyethylene ethanol-iodine complex (100% C12)
2-Alkyl 1-(2-hydroxyethyl)-1 or 3-benzyl-2-imidazolium chloride (C18 as in fatty acids of tall oil)
2-Alkyl 1-(2-hydroxyethyl)-2-imidazoline acetate (as in fatty acids of tall oil)
2-Alkyl 1-(2-hydroxyethyl)-2-imidazoline (C18 as in fatty acids of tall oil)
2-Alkyl 1-hydroxyethyl imidazoline phosphate (100% C13)
Alkyl monoethanol amide (as in fatty acids of coconut oil)
Allyl alcohol
Aluminum phosphide
4-Aminopyridine
Amiton**
Amitrole (C)
Ammonium arsenite (C)

Ammonium fluosilicate
Ammonium sulfamate
Anilinocadmium dilactate
ANTU
Aromatic petroleum derivative solvent
Aromatic petroleum distillate, oil, solvent or hydrocarbons
Arsenic acid (C)
Arsenic pentoxide (C)
Arsenic sulfide (C)
Arsenic trioxide (C)
Auramine
Azinphos**
Azinphos-methyl**
Benzadox, ammonium salt of
1,2-Benzisothiazolin-3-one
Benzoic acid
Benzyl bromoacetate
o-Benzyl-p-chlorophenol
o-Benzyl-p-chlorophenol, potassium salt of
o-Benzyl-p-chlorophenol, sodium salt of
Benzyl diethyl ((2,6-xylylcarbamoyl)methyl)ammonium benzoate
Benzyl(dodecylcarbamoylmethyl)dimethylammonium chloride
Bifenox
1,4-Bis(bromoacetoxy)-2-butene
Bis(2-chloroethyl)ether (C)
trans-1,2-Bis(propylsulfonyl) ethene
Bis(tributyltin) adipate
Bis(tributyltin) dodecenyl succinate
Bis(tributyltin) oxide
Bis(tributyltin) succinate
Bis(tributyltin) sulfide
Bis(tributyltin) sulfosalicylate
Bis(trichloromethyl) sulfone
Boric acid
Bromacil
Bromacil, lithium salt of
Bromacil, sodium salt of
4-Bromoacetoxymethyl-m-dioxolane
1-Bromo-3-chloro-5,5-dimethylhydantoin
beta-Bromo-beta-nitrostyrene
Bromophos**
1,1'-(2'Butenylene) bis(3,5,7-triaza-1-azoniaadamantane chloride)
tert-Butyl hydroperoxide
Butyric anhydride
Cadmium chloride
Calcium arsenate (C)
Calcium arsenite (C)
Calcium cyanide
Calcium cyanamide
Calcium ethylenebisdithiocarbamate (C)
Calcium hypochlorite

Calcium polysulfide
Captafol (T)
Captan (T) (C)
Carbofuran*
Carbon disulfide
Carbon tetrachloride (C)
Carbophenothion** (N)
Carboxin
5-and 6-Carboxy-4-hexyl-2cyclohexane-1-octanoic acid-iodine complex, polyoxyethylene ethanol esters of
Carboxymethyl-1,1-ethylcarboxymethyl-2-undecylimidazolinium hydroxide, disodium salt of
Cetyl diemthyl ethyl ammonium bromide
Cetyl pyridinium bromide
Cetyl pyridinium chloride
Cetyl trimethyl ammonium bromide
Cetyl trimethyl ammonium chloride
Chloramben, and esters and salts (C)
Chlordane (C)
Chlordecone (C) (N) (R)
Chlorfenvinfos**
Chlorinated levulinic acids
Chlorine
Chlorine dioxide
Chlorobenzilate
4-Chloro-2-cyclopentylphenol
4-Chloro-2-cyclopentylphenol, potassium salt of
4-Chloro-2-cyclopentylphenol, sodium salt of
5-Chloro-2-(2,4-dichlorophenoxy)phenol
O-(2-Chloro-2-(2,5-dichlorophenyl)vinyl) O,O-diethyl phosphorothioate**
Chloroethylene bisthiocyanate
Chloroform (C)
Chloromethoxypropylmercuric acetate
1-Chloro-2-nitropropane
4-Chloro-2-phenylphenol
6-Chloro-2-phenylphenol
6-Chloro-2-phenylphenol, potassium salt of
6-Chloro-2-phenylphenol, sodium salt of
2-((p-Chlorophenyl)phenylacetyl)-1,3-indandione
Chloropicrin
4-Chloropyridine n-oxide
Chlorothalonil
4-Chloro-3,5-xylenol
Chlorpyrifos**
Chromic acid
Coal tar (C)
Coal tar acids, coal tar phenols, cresylic acid or cresols
Coal tar neutral oils or coal tar hydrocarbons
Coal tar phenols of coal tar acids
Copper acetoarsenite
Copper arsenate (C)

Copper arsenite (C)
Copper (metallic)
Copper naphthenate
Copper oxide
Copper sulfate
Copper sulfate, basic
Copper-zinc-chromate complex (C)
Coumaphos**
Creosote (wood) (C)
Creosote (coal tar), coal tar cresote or coal tar creosote oils (C)
Creosote oil or coal tar creosote oils (C)
Cresol
Cresylic acid
Crotoxyphos**
Cryolite
Cupric oxide
Cyanuric acid
Cycloheximide
Cyhexatin
DDD (C)
DDT (C)
Demeton**
Dialifor**
Dialkyl ammonium salts
Diamidfos**
Diammonium ethylene bisdithiocarbamate (C)
Diazinon**
1,2-Dibromo-3-chloropropane (C)(R)
2,2-Dibromo-3-nitrilopropionamide
Dichlone
1,2-Dichloropropane, 1,2-dichloropropene and other related compounds
1,3 Dichloropropene
Dichloro-S-triazinetrione
Dichloro-S-triazinetrione, potassium salt
Dichloro-S-triazinetrione, sodium salt of
Dichlorvos**
Dicrotophos**
Didecylmethyl benzyl ammonium chloride
Dieldrin (C)(T)(N)
O,O-Diethyl O-(2-(diethylamino)-6-methyl-4-pyrimidinyl) phosphorothioate**
N3,N3-Diethyl-2,4-dinitro-6-(trifluoromethyl)-m-phenylenediamine
Diethyl diphenyl dichloroethane and related compounds
N,N-Diethyl-m-toluamide, and other isomers
Difenzoquat methyl sulfate
Diisobutylcresoxyethoxyethyl dimethyl benzyl ammonium chloride
Diisobutylphenoxyethoxyethyl dimethyl benzyl ammonium chloride
Dimethyl 3-hydroxyglutaconate dimethyl phosphate**
4,6-Dinitro-o-cresol
4,6-Dinitro-o-cresol, sodium salt of
2,4-Dinitrophenol
Dinoseb, and esters and salts

Dioxathion**
Diphacinone, and esters and salts
Diphenamid
Diphenylamine
Di(phenylmercuri)ammonium propionate
Di(phenylmercury)dodecenylsuccinate
Diphenylstibene 2-ethylhexanoate
Diquat dibromide
Disodium acid methanearsonate
Disulfoton**
DMPA** (N)
Dodecylamine lactate
Dodecylamine salicylate
Dodecylammonium methanearsonate
Dodecylammonium sulfate
Dodecylbenzene sulfonic acid
Dodecylbenzene sulfonic acid, diethanolamine salt of
Dodecylbenzene sulfonic acid, monoethanolamine salt of
Dodecylbenzyl octadecyl dimethyl ammonium chloride
Dodecylbenzyl trimethyl ammonium chloride
Dodecylbenzyl trimethyl ammonium 2-ethylhexoate
Dodecyldimethyl benzyl ammonium chloride
Dodecyldimethyl benzyl ammonium naphthenate
Dodecyldimethyl benzyl ammonium bromide
N-Dodecyldimethyl trichlorobenzyl ammonium chloride
Dodecyldimethyl 2,4,5-trimethyl benzyl ammonium chloride
Dodecylguanidine hydrochloride
Dodecylguanidine terephthalate
Dodine and hydrochloride
Endosulfan
Endothall, and esters and salts
Endrin (T)
EPN** (N)
Ethephon
Ethion**
Ethoprop**
Ethylene
Ethylene dichloride
Ethylene dibromide (C)
Ethylene oxide
Ethyl formate
Ethylmercury phosphate
Ethyl 4-(methylthio)-m-tolyl isopropylphosphoramidate**
4,4'-(2-Ethyl-2-nitrotrimethylene) dimorpholine
Fenbutatin oxide
Fensulfothion**
Ferrous sulfate heptahydrate
Fluoroacetamide
Fluorodifen
Fluosilicic acid
Folpet (T)

Fonofos**
Formaldehyde
Formetanate hydrochloride*
Glutaraldehyde
Glycolic acid
Glycolic acid, postassium salt of
Haloxon** (N)
Heptachlor (C)
2-Heptadecyl-1-methyl-1-(2-(stearoylamido)ethyl) imidazolinium methyl sulfate
1-Heptadecenyl-2-(2-hydroxyethyl) imidazolinium chloride
2-Heptadecenyl imidazoline
2-Heptadecenyl imidazolinium chloride
2-Heptadecenyl-2-imidazoline acetate
Heptadecyl hydroxyethyl imidazoline
Heptadecyl hydroxyethyl imidazolinium chloride
Heptadecyl hydroxyethyl imidazolinium hydrochloride
Hexahydro-1,3,5-tris(2-hydroxyethyl)-S-triazine
Hexahydro-1,3,5-tris(2-hydroxypropyl)-S-triazine
Hexakis (2-methyl-2-phenylpropyl)distannoxane
Hydroiodic acid
Hydrocyanic acid
Hydrofluoric acid
Hydrogen chloride
2-((Hydroxymethyl)amino)-2-methylpropanol
S-(2-Hydroxypropyl) thiomethanesulfonate
Indole-3-butyric acid
Iodine
3-Iodo-2-propynyl butylcarbamate*
Isobutyric acid
2,Isovaleryl-1,3-indandione
2-Isovaleryl-1,3-indandione, calcium salt of
2-Isovaleryl-1,3-indandione, sodium salt of
Lead acetate
Lead arsenate, basic (C)
Lead arsenate, standard (C)
Leptophos** (N)
Lindane
Lithium hypochlorite
Maneb (C)
Mercuric chloride
Mercuric oxide
Mercurous chloride
Mercury (metallic)
Metaldehyde
Methidathion**
Methomyl*
Methyl bromide
Methyldodecylbenzyl trimethyl ammonium chloride 80% and methyldodecyl-
xylylene bis(trimethyl ammonium chloride) 20%
2,2'-Methylene bis(4-chlorophenol)
2,2'-Methylene bis(4-chlorophenol), sodium salt of

2,2'-Methylene bis(4,6-dichlorophenol), sodium salt of
Methylene bis(thiocyanate)
2,2'-Methylene bis(3,4,6-trichlorophenol)
2,2'-Methylene bis(3,4,6-trichlorophenol), disodium salt of
2,2'-Methylene bis(3,4,6-trichlorophenol), monosodium salt of
Methylmercury quinolinolate
Methyl parathion**
Metolachlor
Mevinphos**
Mexacarbate*
Mirex (C)
Monocrotophos**
Nabam (C)
Naled**
Nicotine or nicotine alkaloid
Nicotine sulfate
4-(2-Nitrobutyl)morpholine
2-Nitro-1-butyl phosphate
Nitrofen (C)
2-Nitropropane (C)
Nonylphenoxypolyethoxyethanol-iodine complex
Octyl decyl dimethyl ammonium chloride
Octyl dodecyl dimethyl ammonium chloride
2-N-Octyl-4-isothiazolin-3-one
Oil of citronella
Oxalic acid
Oxamyl*
Paraformaldehyde
Paraquat bis(methylsulfate)
Paraquat dichloride
Parathion**
Parinol
PCNB
Pentachlorophenol
Pentachlorophenol, fatty acid esters of (100 % C6-C20)
Pentachlorophenol, potassium salt of
Pentachlorophenol, zinc salt of alkyl-N-propanediamine (C16-C18)
n-Pentyl valerate
Perfluidone
Petroleum distillate, oils, solvent, or hydrocarbons; also paraffinic hydrocarbons, aliphatic hydrocarbons, paraffin oil
Phenol
Phenylmercuric acetate
Phenylmercuric ammonium acetate
Phenylmercuric ammonium propoionate
Phenylmercuric borate
Phenylmercuric carbonate
Phenylmercuric 2-ethylhexanoate
Phenylmercuric formamide
Phenylmercuric lactate
Phenylmercuric oleate

Phenylmercuric propionate
Phenylmercuric triethanol ammonium lactate
o-Phenylphenol
o-Phenylphenol, alkenyl amine salt of (100% C8-C18)
o-Phenylphenol, alkyl amine-copper salt of (100% C8-C18)
o-Phenylphenol, alkyl amino-zinc salt of (100% C18)
o-Phenylphenol, ammonium salt of
o-Phenylphenol, potassium salt of
o-Phenylphenol, tetradecylamine salt of
Phorate**
Phosazetim**
Phosmet** (T)
Phosphamidon**
Phosphoric acid
Phosphorus
Pindone, and salts
Polyethoxypolypropoxyethanol-iodine complex
Poly(oxyethylene(dimethyliminio)ethylene (dimethyliminio)ethylene dichloride
Polyram (C)
Potassium ammonium ethylene bisdithiocarbamate (C)
Potassium chromate
Potassium cyanate
Potassium dichromate
Potassium N-hydroxymethyl-N-methyldithiocarbamate
Potassium mercuric iodide
Potassium mercuric iodide
Potassium permanganate
Profluralin
Propargite
Propionic acid
Propylene oxide
Pyridylmercuric acetate
N1-(2-Quinoxalinyl)sulfanilamide
Red squill
Silver fluoride
Sodium aluminum fluosilicate
Sodium arsenate (C)
Sodium arsenite (C)
Sodium azide
Sodium bisulfite
Sodium bisulfate
Sodium chlorite
Sodium chromate
Sodium cyanide
Sodium dichromate
Sodium fluoride
Sodium fluoroacetate
Sodium fluosilicate
Sodium hydroxide
Sodium hypochlorite
Sodium pentachlorophenate

Sodium phosphate
Sodium pyroarsenate (C)
Stoddard solvent
Strychnine
Strychnine sulfate
Sulfamic acid
Sulfotepp**
Sulfur
Sulfur dioxide
Sulfuric acid
Sulfuryl fluoride
Tartar emetic
TEPP**
Terbufos**
Terpene polychlorinates
2,4,5-T, and esters and salts (T)
1,1,2,2-Tetrachloroethane (C)
Tetrachloroethylene (C)
2,3,5,6-Tetrachloro-4-(methylsulfonyl)pyridine
Tetrachlorophenols
Tetrachlorophenols, alkyl amine salt (as in fatty acids of coconut oil)
Tetrachlorophenols, potassium salt of
Tetrachlorvinphos** (C)
3,3,4,4-Tetrachlorotetrahydrothiophene-1,1-dioxide (92%) and other
chlorinated thiophene dioxide (8%)
Tetradecylbenzene sulfonate-hypochlorous acid complex
Tetradifon
Tetrahydro-3,4-dimethyl-2H-1,3,5-thiadiazine-2-thione
2-(4-Thiazolyl)benzimidazole
2-(Thiocyanomethylthio)benzothiazole
Thiram (T)
Toxaphene
S,S,S-Tributyl phosphorotrithioate** (N)
S,S,S-Tributyl phosphorotrithioite** (N)
Tributyltin fluoride
Tributyltin monopropylene glycol maleate
Tributyltin neodecanoate
Trichloroacetic acid
Trichloroacetic acid, sodium salt
Trichloroethylene (C)
2,4,5-Trichlorophenol
2,4,5-Trichlorophenol, sodium salt of
2,3,5-Trichloro-4-propylsulfonyl pyridine 36% other chlorinated pyridines
(mono(trichloro)tetra(monopotassiumdichloro)penta-s-triazinetrione
4% inert 60%
Trichloro-S-triazinetrione
alpha, alpha, alpha Trifluoro-4-nitro-m-cresol
Trifluralin (C)
Triforine
3-(Trimethoxysilyl)propyl dimethyl octadecylammonium chloride
Triphenyltin flouride

Triphenyltin hydroxide
Trisodium phosphate
Vinylene bis(thiocyanate)
Warfarin
Warfarin, sodium salt of
Xylene
Zinc ion and manganese ethylene bisdithiocarbamate 80%, A coordination product of manganese 16%, zinc 2%, ethylene bisdithiocarbamate 62% (C)
Zinc mercury chromate (C)
Zinc phosphide
Zinc 2-pyridinethiol 1-oxide
Zineb (C)
Ziram

(C) Designates suspected carcinogen
(N) Designates suspected neurotoxin
(R) Designates suspected reproductive effect
(T) Designates suspected teratogen

Group II

alpha-Alkyl -omega-hydroxypoly(oxyethylene)(100% C12-C15)
Alkyl poly(oxypropylene) poly(oxyethylene)-iodine complex (100% C12-C15)
Alkyl 1,3-propanediamine (53% C12, 19% C14, 8.5% C16, 7% C8, 6.5% C10, 6% C18)
Alkyl 1,3-propylenediamine (as in fatty acids of coconut oil)
Alkyl 1,3-propylenediamine (42% C12, 26% C18, 15% C14, 8% C16, 5% C10, 4% C8)
Alkyl 1,3-propylenediamine (47% C12, 18% C14, 10% C18, 9% C10, 8% C16, 8% C8)
N-Alkyl 1,3-propylenediamine acetate (as in coconut oil fatty acids)
Alkyl 1,3-propylenediamine acetate (47% C12, 18% C14, 10% C18, 9% C10, 8% C16, 8% C8)
N-Alkyl 1,3-propylenediamine adipate (as in fatty acids of coconut oil)
Alkyl 1,3-propylenediamine monobenzoate (as in fatty acids of coconut oil)
Allethrin
Ametryn
Amitraz
Ammonium polysulfides
Antimycin A
B. lentimorbus
B. popilliae
B. thuringiensis
BAN
Barium carbonate
Barium metaborate
Bentazon, sodium salt of
Benzaldehyde

4-Benzothienyl methylcarbamate*
Benzyl alcohol
Benzyl benzoate
(5-Benzyl-3-furyl)methyl 2,2-dimethyl-3-(2-methylpropenyl)cyclopropane-carboxylate
2,3,4,5-Bis(2-butylene)tetrahydro-2-furaldehyde
1,1-Bis(chlorophenyl)-2,2,2-trichloroethanol
Bis(tripropyltin) oxide
Bone oil
2-Bromo-4'-hydroxyacetophenone
Bromoxynil octanoate
Bufencarb*
2-Butanol
2-Butoxyethanol
Butoxypolypropoxypolyethoxyethanol-iodine complex
Butralin
tert-Butyl alcohol
sec-Butylamine
tert-Butyl dimethyltrithioperoxycarbamate
Cacodylic acid
Cacodylic acid, sodium salt of
Cadmium-calcium-copper-zinc-sulfate-chromate complex
Cadmium carbonate
Cadmium sebacate
Cadmium succinate
Cadmium sulfate
Calcium propanearsonate
Calcium propionate
Carbaryl*
Cetyl alcohol
n-Cetyl-n-ethyl morpholinium ethylsulfate
Chloranil
Chlordimeform
Chlordimeform hydrochloride
2-Chloroallyl diethyldithiocarbamate
1-(3-Chloroallyl)-3,5-7-triaza-1-azoniaadamantane chloride
S-(4-Chlorobenzyl) diethylthiocarbamate
4-Chloro-m-cresol
2-((4-Chloro-6-(ethylamino)-S-triazine-2-yl)amino)-2-methylpropionitrile
2-Chloroethyl trimethyl ammonium chloride
2-Chloro-n-isopropylacetanilide
5-Chloro-2-mercaptobenzothiazole, lauryl pyridinium salt of
o-Chlorophenol
o-Chlorophenol, sodium salt of
p-Chlorophenoxyacetic acid
p-Chlorophenoxyacetic acid, diethanolamine salt of
2-(m-Chlorophenoxy)propionamide
2-(m-Chlorophenoxy)propionic acid
2-(m-Chlorophenoxy)propionic acid, sodium salt of
p-Chlorophenyl diiodomethyl sulfone
2-Chloro-4-phenylphenol

2-Chloro-4-phenylphenol, potassium salt of
2-Chloro-4-phenylphenol, sodium salt of
4-Chloro-2-phenylphenol, potassium salt of
4-Chloro-2-phenylphenol, sodium salt of
4 and 6-Chloro-2-phenylphenol, diethanolamine salt of
3-Chloro-p-toluidine hydrochloride
d-trans-Chrysanthemum monocarboxylic acid ester of d-2-allyl-4-hydroxy-3-methyl-2-cyclopenten-1-one
Copper carbonate
Copper oleate
Copper 8-quinolinolate
Copper salts of fatty and rosin acids
Crufomate**
Cube resins
3-Cyclohexyl-6-(dimethylamino)-1-methyl-1,3,5-triazine-2,4(1H,3H)-dione
Cythioate**
2,4D
2,4-D, alkanolamine salts of ethanol and isopropyl series of
2,4-D, butyl ester of
2,4-D, dimethylamine salt of
2,4-D, isooctyl (2-ethylhexyl) ester of
2,4-D, isooctyl (2-octyl) ester of
2,4-D, isopropyl ester of
2,4-D, lithium salt of
2,4-D, n-oleyl-1,2-propylenediamine salt of
2,4-D, potassium salt of
2,4-D, triethanolamine salt of
2,4-DB
2,4-DB, dimethylamine salt of
1-Decanol
Demeton-S-methyl**
Desmedipham
N,N-Diallyl-2-chloroacetamide
Dicapthon**
Dichlobenil
Dichlofenthion**
o-Dichlorobenzene
p-Dichlorobenzene
2,4-Dichloro-6-(o-chloroanilino)-5-triazine
1,3-Dichloro-5,5-dimethylhydantoin
2,6-Dichloro-4-nitroaniline
4,6-Dichloro-2-phenylphenol
4,6-Dichloro-2-phenylphenol, potassium salt of
3',4'-Dichloropropionanilide
Dichlorprop, and esters and salts
Diethyl dithiobis (thionoformate)
Diethylene glycol monomethyl ether
1,2-Dihydro-3,6-pyridazinedione
1,2-Dihydro-3,6-pyridazinedione, diethanolamine salt of
1,2-Dihydro-3,6-pyridazinedione, potassium salt of
Diiodomethyl p-tolyl sulfone

Diisobutyl ketone
Dimethoate**
p-(Dimethylamino) benzenediazo sodium sulfonate
2,2-Dimethyl-1,3-benzodioxol-4-ol methylcarbamate*
Dimethyl tetrachloroterephthalate
Dimethyl(2,2,2-trichloro-1-hydroxyethyl)phosphonate ester of butyric acid**
2,4-Dinitrochlorobenzene
Diphenylacetonitrile
Disodium 2,2'-thiobis(4,6-dichlorophenate)
Diuron
Epichlorohydrin
Erbon
Ethanol
6-Ethoxy-1,2-dihydro-2,2,4-trimethyl quinoline
5-Ethoxy-3-(trichloromethyl)-1,2-4-thiadiazole
S-Ethyl dipropylthiocarbamate
Ethylenediamine
S-Ethyl hexahydro-1H-azepine-1-carbothioate
Eugenol
Famphur**
Fatty alcohols (54.5% C10, 45.1% C8, 0.4% C6)
Fatty alcohols (56% C10, 42% C8, 1.5% C12, 0.5% C6)
Fatty alcohols (55.10% C10, 42.88% C8, 1.01% C6, 1.01% C12)
Fenitrothion**
Fenthion**
Fluchloralin
Glyphosate, isopropylamine salt of
Hexachlorobenzene
Hexachlorocyclohexane, technical
Hexachlorocyclopentadiene
Hexachloroethane
2-((Hydroxymethyl)amino)ethanol
2-(Hydroxymethyl)-2-nitro-1,3-propanediol
3-Hydroxy-N,N,5-trimethylpyrazole-1-carboxamide dimethylcarbamate*
Isobornyl acetate
Isobornyl thiocyanoacetate
Isobutanol
Isopropanol
o-Isopropoxyphenyl methylcarbamate*
Isopropyl N-(3-chlorophenyl)carbamate
Isopropyl N-phenylcarbamate
Karbutilate
Malathion**
MCPA, and esters and salts
MCPB, and esters and salts
Mecoprop, and esters and salts
Menthol
2-Mercaptobenzothiazole, and esters and salts
Methanol
Methazole
Methiocarb*

Methlated aromatic petroleum derivative
Methylated naphthalenes
Methylcarbophenothion**
2,2'-Methylene bis(4,6-dichlorophenol)
Methylene chloride
Methyl esters of fatty acids (C8 - C12)
Methyl ethyl ketone
Methyl isobutyl ketone
Methyl isothiocyanate
Methyl nonyl ketone
4-(Methylthio)-3,5-xylyl methylcarbamate*
Mineral oil, mineral seal oil, white mineral oil
Monuron
Monuron trichloroacetate
1-Naphthaleneacetic acid, and esters and salts
(2-Naphthyloxy) acetic acid
N-1-Naphthylphthalamic acid, and esters and salts
Neodecanoic acid
Nitrapyrin
N-9-Octadecenyl-1,3-propanediamine monogluconate
1-Octanol
Oleic acid
Ovex
10,10'-Oxybisphenarsazine
10,10'-Oxybisphenoxarsine
Peroxyacetic acid
Phenmedipham
Phenothiazine
Phenthoate**
2-Phenylethanol
2-Phenylethyl propionate
Phosalone**
Pine oil
Pine tar
Pine tar oil
Piperonyl butoxide
Polybutene
Potassium gibberellate
Prometon
Pyrethrins
Pyrethrum powder other than pyrethrins
N-3-Pyridylmethyl-N'-p-nitrophenylurea
Ronnel**
Rotenone
Sabadilla alkaldids
Silicon dioxide
Silvex, and esters and salts
Simazine
Sodium N,N-dimethyl dithiocarbamate
Sodium methyldithiocarbamate
Sodium propionate

Sodium 2-pyridinethio 1-oxide
Streptomycin
Streptomycin sulfate
Sulfoxide
Temephos**
1,2,4,5-Tetrachloro-3-nitrobenzene
Tetraglycine hydroperiodide
Tetraiodoethylene
0,0,0,0-Tetrapropyl dithiopyrophosphate**
Thiobencarb
3,4'-5-Tribromosalicylanilide
Tributyltin acetate
Tributyltin benzoate
Tributyltin chloride
Tributyltin chloride complex of ethylene oxide condensate of abietylamine
Tributyltin resinate
Trichlorfon**
2,3,6-Trichlorobenzoic acid and related polychlorobenzoic acids, dimethlamine salt of
Triethylene glycol
Trimethylbenzyl ammonium resin, polybromide form
3,4,5 and 2,3,5-Trimethylphenyl methylcarbamate*
Xylene range aromatic solvent
Zinc fluosilicate
Zinc naphthenate
Zinc sulfate
Zinc sulfate, basic

Group III***

Acephate**
Acetic acid
Acetone
Acrylic polymer resins
Allantoin
Allyl isothiocyanate
Aluminum chloride
Aluminum chlorohydroxy allantoinate
Aluminum hydroxybenzenesulfonate
Aluminum sulfate
Amidithion**
4-Amino-6-tert-butyl-3-(methylthio)-as-triazine-5(4H)-one
Ammonia
Ammonium alum
Ammonium carbonate
Ammonium citrate
Ammonium hydroxide
Ammonium hydroxide - C8 fatty acid silver complex
Ammonium isobutyrate

Ammonium lauryl sulfate
Ammonium oleate
Ammonium oxalate
Ammonium sulfate
Ammonium thiosulfate
Amyl acetate
o-sec-Amylphenol
p-tert-Amylphenol
p-tert-Amylphenol, potassium salt of
p-tert-Amylphenol, sodium salt of
Anabasine
Ancymidol
Anthracene oil
Asphalt
Asulam, sodium salt of
Atrazine
Benomyl
Bensulide**
d-trans(5-Benzyl-3-furyl) methyl 2,2-dimethyl-3-(2-methylpropenyl)
cyclopropane carboxylate
Binapacryl
Biphenyl
2,2-Bis(4-chlorophenyl)ethanol
2,6-Bis((dimethylamino)methyl)cyclohexanone
N,N-Bis(2-hydroxyethyl) lauramide
Bismuth subgallate
Borax
Butoxypolypropylene glycol
beta-Butoxy beta'-thiocyano diethyl ether
N-Butylacetanilide
Butyl 3,4-dihydro-2,2-dimethyl-4-oxo-1,2H-pyran-6-carboxylate
1,3-Butylene glycol
2-Butyl-2-ethyl-1,3-propanediol
N-Butyl-N-ethyl-alpha,alpha,alpha-trifluoro-2,6-dinitro-p-toluidine
p-tert-Butylphenol
p-tert-Butylphenol, potassium salt of
p-tert-Butylphenol, sodium salt of
1-(p-tert-Butylphenoxy)-1-methylethyl 1-chloroethyl sulfite
Butyl p-hydroxybenzoate
Calcium acid methanearsonate
Calcium chloride
Calcium chlorate
Calcium naphthenate
Calcium phosphate
Calcium thiosulfate
Camphor
Camphor oil
Canadian balsam
Capsaicin (in oleoresin of capsicum)
Carbon
Castor oil

Cedar leaf oil
Cedarwood oil
Chloramine B
Chloramine T
Chlorbromuron
Chlorobutanol
Chloroneb
O-(3-Chloro-4-nitorphenyl) O,O-dimethyl phosphorothioate**
p-Chlorophenyl phenyl sulfone
p-Chlorophenyl 2,4,5-trichlorophenyl sulfide
Chloropropylate
5-Chlorosalicylanilide
2-Chloro-2'-(2,4,6-trichlorophenoxy)diethyl ether
Chloroxuron
6-(and 2)-Chloro-3,4-xylyl methylcarbamate*
Chromic acetate
Citral
Citric acid
Cobalt naphthenate
Cod liver oil
Copper acetate
Copper ammonium carbonate
Copper chloride, basic
Copper chloride (dihydrate)
Copper dehydroarietyl ammonium 2-ethylhexoate
Copper ethylenediaminotetraacetate
Copper 2-ethylhexoate
Copper hydroxide
Copper hydroxynaphthenate
Copper linoleate
Copper oxalate
Copper oxychloride
Copper oxychloride sulfate
Copper pyrophosphate
Copper salts of the acids of tall oil
Copper sulfate monohydrate
Copper sulfate pentahydrate
Cottonseed oil
Cupric ferric subsulfate complex
Cupric zinc sulfate complex, basic
Cuprous thiocyanate
Cyanogen chloride
Cyclohexane
Cyclohexanone
2-Cyclohexylcyclohexanol
Cyprazine
2,4-D, alkyl amine salt of (as in tall oil fatty acids)
2,4-D, alkyl amine salt of (C12)
2,4-D, alkyl amine salt of (C13)
2.4-D, alkyl amine salt of (C14)
2,4-D, ammonium salt of

2,4-D, amyl(pentyl) ester of
2,4-D, butoxyethoxypropyl ester of
2,4-D, butoxyethyl ester of
2,4-D, butoxypolyethoxypropyl ester of
2,4-D, butoxypropyl ester of
2,4-D, diethanolamine salt of
2,4-D, diethylamine salt of
2,4-D, diethylethanolamine salt of
2,4-D, diisopropylamine salt of
2,4-D, N,N-dimethyloleylamine salt of
2,4-D, N,N-dimethyl oleyl-linoleyl amine salt of
2,4-D, dipropylene glycol isobutyl ether ester of
2,4-D, ethanolamine salt of
2,4-D, ethoxyethoxyethyl ester of
2,4-D, ethoxyethoxypropyl ester of
2,4-D, ethylamine salt of
2,4-D, ethylene gylcol butyl ether ester of
2,4-D, ethyl ester of
2,4-D, heptylamine salt of
2,4-D, isooctyl (2-ethyl-4-methylpentyl) ester of
2,4-D, isopropanolamine salt of
2,4-D, isopropylamine salt of
2,4-D, isobutyl ester of
2,4-D, linoleylamine salt of
2,4-D, methylamine salt of
2,4-D, methyl ester of
2,4-D, morpholine salt of
2,4-D, octylamine salt of
2,4-D, oleylamine salt of
2,4-D, polyethylene gylcol 200 ester of
2,4-D, polypropoxybutyl ester of
2,4-D, polypropylene glycol ester of
2,4-D, propylamine salt of
2,4-D, propylene glycol butyl ether ester of
2,4-D, propylene glycol isobutyl ether ester of
2,4-D, propylene glycol ester of
2,4-D, sodium salt of
2,4-D, triethyamine salt of
2,4-D, triisopropanolamine salt of
2,4-D, trimethylamine salt of
2,4-D, tripropyleneglycol isobutyl ether ester of
2,4-D, tetrahydrofurfuryl ester of
Dalapon
Dalapon, diethyleneglycol ester of
Dalapon, magnesium salt of
Dalapon, sodium salt of
Daminozide
2,4-DB, butoxyethanol ester of
2,4-DB, butyl ester of
2,4-DB, isooctyl ester of
Decachlorobis(2,4-cyclopentadiene-1-yl)

Dehydroabietylamine
Dehydroabietylamine acetate
Dehydroabietylamine-ethylene oxide condensate
Dehydroabietylammonium pentachlorophenoxide
Dehydroabietylammonium phenoxide
Derris resins
Dextrin
Diacetone alcohol
1,6-Diamino-2,2-difluorohexane
20,25-Diazachlolestenol dihydrochloride
2,3-Dibromopropionaldehyde
3,5-Dibromosalicylanilide
4',5-Dibromosalicylanilide
3,5-Dibromo-3'-(trifluromethyl)salicylanilide
2,6-Di-tert-butyl-p-cresol
Dibutyl succinate
2,6-Di-tert-butyl-p-tolyl methylcarbamate*
Dicamba, and esters and salts
Dichlormate
S-(2,3-Dichloroallyl) diisopropylthiocarbamate
Dichlorodifluoromethane
3,4-Dichloro-N-(1,1-dimethyl-2-propynyl)benzamide
4,4'-Dichloro-alpha-methylbenzhydrol
2',5-Dichloro-4'-nitrosalicylanilide, 2-aminoethanol salt of
2,4'Dichlorophenyl ester of benzenesulfonic acid
p-(N,N-Dichlorosulfamoyl)benzoic acid
Dicryl
Dicyclopentadiene-linseed oil copolymer
Di(dehydroabietyl)amine acetate
Diethanolamine myristate-iodine complex
2-(2-(2-N,N-Diethylamino)ethoxy)ethoxy)bornane
N,N-Diethyl-2-(1-naphthalenyloxy)propionamide
Diethyl 4,4'-O-phenylenebis (3-thioallophanate)
Dihydroabietylamine acetate
5,10-Dihydro-5,10-dioxonaphtho(2,3-8)-p-dithiin-2,3-dicarbonitrile
Dihydrorotenone
N,N-Di(hydroxyethyl) alkyl amine (as in soybean fatty acids)
5,7-Diiodo-8-quinolinol
Diisobutylphenoxyethanol
Dilauryl dimethyl ammonium bromide
Dimethrin
2-(Dimethylamino)-4,5-dimethyl-4-pyrimidinyl dimethylcarbamate*
4-(Dimethylamino)-m-tolyl methylcarbamate*
2,6-Dimethyl-m-dioxan-4-ol acetate
N,N-Dimethyldodecylamine acetate
Dimethyl isopropylaminophenanthrene
Dimethyl ((4-methyl-1,3-phenylenebis(iminocarbonyl-1H-benzimidazole-1,2-diyl))biscarbamate*
N'(2,4-Dimethylphenyl)-N-(((2,4-dimethylphenyl)imino)methyl)-N-methanimidamide
Dimethyl phthalate
2,4-Dinitro-6-octyl phenyl crotonate, 2,6-dinitro 4-octyl phenyl crotonate and nitrooctylphenols (principally dinitro)

Di-n-propylmaleate isosafrole condensate
Dioctyl sodium sulfosuccinate
Dipropetryn
Dipropylene glycol
Dipropylene glycol methyl ether
Dipropyl insocinchomeronate
Disodium cyanodithioimidocarbonate
Disodium dihydroxyethyl ethylenediamine diacetate
Disodium 4-dodecyl-2,4'-oxydibenzenesulfonate
Disodium N-(2-hydroxyethyl)iminodiacetate
Disodium monoethanolamine phosphate
Disodium octaborate tetrahydrate
Disodium 2,2'-oxybis(4-dodecylbenzenesulfonate)
2,2'-Dithiobisbenzothiazole
beta,beta'-Dithiocyano diethyl ether
Dodecyldiethylamine
Dried blood
Essential oils or perfume
Ester gums
Ethanolamine
Ethiolate
2-Ethoxyethyl-p-methoxycinnamate
Ethoxylated monoethanolamine of lauric acid
Ethoxylated lanolin
Ethyl acetate
Ethyl p-aminobenzoate
2-(Ethylamino)-4-(isopropylamino)-6-methoxy-S-triazine
S-Ethyl cyclohexylethylthiocarbamate*
S-Ethyl diisobutylthiocarbamate
Ethyl alpha-((dimethoxyphosphinothionyl)thio) benzeneacetate
Ethylenediaminetetraacetic acid, and esters and salts
Ethylene glycol
Ethylene glycol bis(trichloroacetate)
Ethylene glycol ether of pinene
Ethylene glycol monomethyl ether
1-Ethyl-2-heptadecenyl-1-(2-hydroxyethyl) imidazolinium bromide
2-Ethyl-1,3-hexanediol
2-Ethylhexoate salt of magnesium quinolinolate
Ethyl p-hydroxybenzoate
N-(1-ethylpropyl)-3,4-dimethyl-2,6-dinitrobenzenamide
Fenuron
Ferbam
Ferric sulfate
Ferrous ammonium sulfate
Fluoridamid, diethanolamine salt of
Fluometuron
Fospirate**
Fuel oil
Fumaric acid
Furfural

Gibberellic acid
Gluconic acid
Glycerol
Glyceryl p-aminobenzoate
Glyphosine
Gum resins
Hardwood distillate
Hardwood oil
Heavy aromatic naphtha
Hexachloroacetone
3,4,5,6,7,7-Hexachloro-N-(methylmercuri)-1,2,3,6-tetrahydro-3,6-endomethano-phthalimide
Hexahydro-1,3,5-triethyl-S-triazine
Hexamethylenetetramine
1,1'-Hexamethylene bis(5-(p-chlorophenyl)biguanide)diacetate
n-Hexanol
Hydrocortisone
Hydrogenated castor oil
Hydroxyethylenediaminetetraacetic acid, sodium salt of
Hydroxyethylethylenediaminetriacetic acid, trisodium salt of
1-(2-Hydroxyethyl)-2-heptadecenylimidazoline
2-Hydroxyethyl octyl sulfide
Ichthammol
Iodine-potassium iodide complex
Isocil
Isooctyl phenoxy polyethoxy ethanol
Isophorone
Isopropalin
Isopropyl-o-cresol
Isopropyl lanolin
Isopropyl myristate
m-Isopropylphenyl methylcarbamate*
Isothymoxy chloroethyl ether
Juniper tar
Kerosene or deodorized base oil
Lanolin
Larkspur alkaloid
N-Lauroyl ester of colaminoformylmethylpyridinium chloride
Lauryl alcohol
Lauryl diethanolamide
N-Lauryl diethylene triamine
Lauryl isoquinolinium bromide
Lauryl methacrylate
Limonene
Linseed oil
Linuron
Lithium stearate
Magnesium chloride
Magnesium fluosilicate
Magnesium lauryl sulfate
Magnesium silicate

Magnesium sulfate
Magnesium trichloroacetate
Malachite green
Manganous benzothiazylmercaptide
Manganous dimethyl dithiocarbamate
Methapyrilene hydrochloride
Methoprene
Methoxychlor
1-Methoxy-4-propenylbenzene
Methyl 2-chloro-9-hydroxyfluorene-9-carboxylate 65-70%, methyl 9-hydroxy-fluorene-9-carboxylate 11-13%, methyl 2,7-dichloro-9-hydroxyfluorene-9-carboxylate 12-19%
Methyl-2,3-dibromopropionate
Methyl 3-((dimethoxy phosphinyl)oxy crotonate, alpha isomer and related compounds
Methylene blue
Methyl p-hydroxybenzoate
2-Methyl-1-naphthaleneacetamide
2-Methyl-1-naphthaleneacetic acid
Methyl napthalene sulfonate
2-Methyl-2,4-pentanediol
3-(2-Methylpiperidino)propyl 3,4-dichlorobenzoate
6-Methyl-2,3-quinoxalinedithiol cyclic S,S-dithiocarbonate
Methylrosaniline chloride
Methyl salicylate
4-(Methylsulfonyl)-2,6-dinitro-N,N-dipropylaniline
2,2'-(1-Methyltrimethylenedioxy)bis(4-methyl-1,3,2-dioxaborinane
Metobromuron
Mineral spirits
Mixed alkyl pyridines
Monoammonium acid methanearsonate
Monoethanolamides of the fatty acids of coconut oil
Monoethanolamine laurate
Monoethanolamine oleate
Monosodium acid methanearsonate
Monosodium phosphate
Morpholine
Morpholine polyethoxyethanol
1-Naphthaleneacetamide
Naphthalene
beta-Naphthol
Neburon
Neomycin
Neomycin sulfate
Nickel sulfate hexahydrate
Nitrilotriacetic acid, trisodium salt of
Nitrocellulose
N(alpha-(1-Nitroethyl)benzyl)ehhylenediamine, potassium salt of
2-Nitro-2-methyl-1,3-propanediol
p-Nitrophenol
Nonylphenoxypolyethoxyethanol

Norbormide
Norea
Norflurazon
Octachlorohexahydro-4,7-methanoisobenzofuran
Octamethylpyrophosphoramide
Octanoic acid ester of 3,5-dibromo-4-hydroxybenzonitrile
Octylammonium methanearsonate
N-Octyl bicyclohepten dicarboximide
Octylphenol
Octylphenoxypolyethoxyethanol-iodine complex
N-Octyl sulfoxide of isosafrole
Oil camphor sassafrassy
Oil of anise
Oil of eucalyptus
Oryzalin
2,2'-Oxybis(4,4,6-trimethyl-1,3,2-dioxaborinane)
Oxycarboxin
Oxyethylated-tert-butylphenol
Oxytetracycline
Paloja
Pentachlorodihydroxytriphenylmethanesulfonic acid
n-Pentane
1-Pentanethiol
Pentasodium diethylenetriamine acetate
Piperazine-carbon disulfide complex
Petroleum resins
Phenarsazine chloride
Phenolic - tung oil varnish
Phenolsulfonic acid
3-Phenyl-1,1-dimethylurea trichloroacetate
N-(1-Phenyl-2-nitropropyl) piperazine, potassium salt of
Picloram, and esters and salts
Pinene
Piperazine dihydrochloride
Piperonal bis(2-(2-butoxethoxy)ethyl) acetal
Polyamidohygrostreptin
Polychlorobicyclopentadiene isomers(chlorine content 60-62% or 62-64%)
Polyethoxypolypropoxypolyethoxyethanol,N-alkyl di(beta-hydroxyethyl) benzyl ammonium chloride-iodine complex (54% C12, 18% C14, 9% C18, 9% C16, 5% C10, 5% C8)
Polyethoxypolypropoxypolyethoxyethanol-N-alkyl dimethyl-3,4-dichlorbenzyl ammonium chloride-iodine complex (50% C12, 30% C14, 17% C16, 3% C18)
Polyethoxypolypropoxypolyethoxy ethanol-iodine complex
Polyethylene
Polyethylene condensate with abietylamine
Polyethylene glycol distearate
N-Polyethylene polyamine (18-mole) N-oleylamine hydrochloride
Polyisobutylene
Polymerized blyceryl oleate
Polyoxyethylene sorbitan monolaurate
Polyoxyethylene sorbitan monooleate

Polyoxyethylene sorbitol mixed ether ester of
Polyoxyethylene sorbitol oleate-laurate
Polypropylene glycol
Polyvinylpyrrolidone
Polyvinylpyrrolidone-iodine complex
Potassium bisulfate
Potassium bromide
Potassium carbonate
Potassium dodecylbenzene sulfonate
Potassium fish oil soap
Potassium hydroxide
Potassium iodate
Potassium iodide
Potassium laurate
Potassium N-methyldithiocarbamate
Potassium myristate
Potassium nitrate
Potassium peroxymonosulfate
Potassium persulfate
Potassium phosphate, monobasic
Potassium phosphate, tribasic
Potassium polysulfide
Potassium ricinoleate
Potassium tetrathionate
Potassium thiosulfate
Potassium toluene sulfonate
Potassium xylene sulfonate
Prometryn
Propanol
Propazine
S-Propyl butylethylthiocarbamate
S-Propyl dipropylthiocarbamate
Propylene dichloride
Propylene gylcol
Propyl 4-hydroxybenzoate
Propyl 4-hydroxybenzoate, sodium salt of
Putrescent whole egg solids
Pyrazon
Pyridine
8-Quinolinol
8-Quinolinol benzoate
8-Quinolinol sulfate
Quinone
2,3-Quinoxalinedithiol cyclic trithiocarbonate
Rosin oil
Rutralin
Ryania speciosa, powdered stems of
Ryanodine
Safrole
Salicylanilide
Selenium disulfide

Sesame oil
Siduron
Silica gel
Silver
Silver salt of partially polymerized mannuronic acid
Silver thiuronium acrylate co-polymer
Soap
Sodium alkyl benzene sulfonate (100% C9)
Sodium benzoate
Sodium bromide
Sodium carbonate
Sodium chloride
Sodium chlorate
Sodium 5-chloro-2-(4-chloro-2-(3-(3,4-dichlorophenyl)oreido)phenoxy)
benzene sulfonate
Sodium n-cyclohexyl-n-palmitoyl taurate-iodine complex
Sodium decyl diphenylether disulfonate
Sodium decylbenzene sulfonate
Sodium dehydroacetate
Sodium diacetate
Sodium di(1-alkenyl)phenoxybenzene disulfonate (100% C9-C10)
Sodium dihydroxyethylglycine
Sodium diisopropylnaphthalene sulfonate
Sodium di(monoethanolamine)phosphate
Sodium dodecylbenzenesulfonate
Sodium dodecylbenzenesulfonate-iodine complex
Sodium dodecyl diphenyl oxide sulfonate
Sodium ethylmercurithiosalicylate
Sodium glcolate
Sodium laurate
Sodium N-lauryl sarcosinate
Sodium lauryl sulfate
Sodium metaborate
Sodium metasilicate
Sodium methyl oleyl taurate
Sodium methylundecyl benzene sulfonate
Sodium mono(1-alkenyl)phenoxybenzene disulfonate (100% C9-C10)
Sodium mono and dimethyl naphthalene sulfonate
Sodium nitrate
Sodium nitrite
Sodium octylbenzene sulfonate
Sodium oleate
Soidum perborate
Sodium persulfate
Sodium phenate
Sodium o-phenylphenate
Sodium p-phenylphenate
Sodium polyethoxyethyl dodecylsulfate
Sodium polysulfide
Sodium salt of petroleum sulfonic acid
Sodium silicate

Sodium sulfate
Sodium sulfite
Sodium sulforicinoleate
Sodium tetrachlorophenate
Sodium thiosulfate
Sodium tridecylbenzene sulfonate
Sodium tripolyphosphate
Sodium xylene sulfonate
Sorbic acid
Sorbic acid, potassium salt of
Soybean oil
Sperm oil
Squalane
Sulfacetamide
Sulfanilamide
Sulfathiazole
Sulfonated cresol
Sulfonated oleic acid, sodium salt of
Sulfonated vegetable oil
Tannic acid
Tar
Tebuthiuron
Terbacil
Terbuthylazine
Terbutryn
Terpineols
Teramaycin or oxytertracycline hydrochloride
Tetracaine hydrochloride
1,3,4,6-Tetrachloroglycoluril and related compounds
3,3',4',5-Tetrachlorosalicylanilide
Tetrachlorothiophene
Tetrahydroabietylamine acetate
Tetrahydro-3,4-dimethyl-2H-1,3,5-thiadiazine-2-thione, sodium salt of
Tetralin
Tetramethrin
Tetrapotassium pyrophosphate
Tetrasodium ethylene diaminetetraacetate
Tetrasodium pyrophosphate
Thallium sulfate
2,2'-Thiobis(4-chlorophenol)
2,2'-Thiobis(4-chloro-6-methylphenol)
2,2'-Thiobis(4,5-dichlorophenol)
beta-Thiocyanoethyl esters of mixed fatty acids (C10-C18)
Thionazin**
Thiophanate-methyl*
Thymol
Thymoxydichloroacetic acid
Tobacco dust
Toluene
Toluene sulfonic acid
Toluene sulfonic acid, sodium salt of

Tributyl-2,4-(dichlorobenzyl)phosphonium chloride
Tributyltin isopropyl succinate
Tributyltin linoleate
Tributyltin salicylate
S-2,3,3-Trichloroallyl diisopropylthiocarbamate
1,2,4-Trichlorobenzene
2,3,6-Trichlorobenzoic acid
2,3,6-Trichlorobenzoic acid, sodium salt of
Trichlorobenzyl chloride
1-((2,3,6-Trichlorobenzyl)oxy)-2-propanol
3,4,4'-Trichlorocarbanilide
1,1,1-Trichlrooethane
Trichloromonofluoromethane
Trichloromelamine
2,4,6-Trichlorophenol, potassium salt
2,3,6-Trichlorophenylacetic acid
2,3,6-Trichlorophenylacetic acid, ammonium salt of
2,3,6-Trichlorophenylacetic acid, dimethylamine salt of
2,3,6-Trichlorophenylacetic acid, sodium salt of
2,4,5-Trichlorophenol, potassium salt
1,4',5'-Trichloro-2'-(2,4,5-trichlorophenoxy)methanesulfonanilide, sodium salt of
Tricosene
Triethanolamine
Triethanolamine dodecylbenzene sulfonate
Triethanolamine laurate
Triethanolamine myristate
Triethanolamine octylsulfate-iodine complex
Triethanolamine oleate
Triethanolamine salt of lauryl sulfate
Triethanolamine sulfonate tridecylpolyoxyethyleneethanol-bromine complex
2,3,5-Triiodobenzoic acid
2,3,5-Triiodobenzoic acid, dimethylamine salt of
Triisopropanolamine
Triisopropylamine
2,2,4-Trimethyl-1,3-pentanediol
Turkey red oil or sulfonated castor oil
Turpentine
Tyrothricin
Undecylenic acid
Urea
Vegetable wax
2,4-Xylenesulfonic acid
2,4-Xylenol
Zinc chloride
Zinc dehydroabietylammonium 2-ethylhexoate
Zinc 2-ethylhexoate
Zinc oxide
Zinc phenol sulfonate
Zinc 8-quinolinolate
Zinc resinate

Ziram, cyclohexylamine complex
Zirconium oxide

*Designates carbamate insecticides that require baseline RBC ChE monitoring only, as stated in Chapter I, section 1, part a(5).
**Designates organophosphorus insecticides that require baseline and routine RBC ChE monitoring as stated in Chapter I, section 1, parts a(5) and C.
***Approximately 350 compounds in (group III were placed there by default; ie, there were no data on which to base their classification in another group. (See Chapter 6 for further explanation).

X. APPENDIX II

METHODS FOR BIOCHEMICAL DETERMINATION OF CHOLINESTERASE ACTIVITY IN BLOOD

The method of Wolfsie and Winter [340], a micromodification of the Michel method [341], is recommended for the measurement of cholinesterase (ChE) activity in workers exposed to organophosphorus (OP) insecticides, but not carbamate insecticides.

Reagents

All reagents should be at least American Chemical Society reagent grade.

(a) Buffer Solution I (for erythrocytes)

For 1 liter of buffer, dissolve 4.1236 g sodium barbital (0.02 M), 0.5446 g potassium orthophosphate, di-H (0.004 M), and 44.730 g potassium chloride (0.60 M) in 900 ml of distilled water; 28.0 ml of 0.1 N hydrochloric acid is added while shaking the solution, and the flask is brought to volume with distilled water. The pH of Buffer I should be 8.10 at 25 C.

(b) Buffer Solution II (for plasma)

For 1 liter of buffer, dissolve 1.2371 g sodium barbital

(0.006 M), 0.1361 g potassium orthophosphate, di-H (0.001 M), and 17.535 g sodium chloride (0.30 M) in 900 ml of distilled water and add 11.6 ml of 0.1 N hydrochloric acid before bringing to volume. The pH of Buffer II should be 8.00 at 25 C.

The pH of the buffer solutions will decrease over a period of several weeks. The pH should be checked before using and, if it has dropped more than 0.03 pH units, it should be discarded and a fresh solution made.

(c) Acetylcholine Substrate (for erythrocytes)

This is 0.11 M acetylcholine chloride (2.000 g in 100 ml of distilled water).

(d) Acetylcholine Substrate (for plasma)

This is 0.165 M acetylcholine chloride (3.000 g in 100 ml of distilled water).

A few drops of toluene are added to each acetylcholine substrate solution as a preservative, and the solutions are refrigerated when not in use. The acetylcholine solutions should not be retained for more than 1 week.

(e) Saponin Solution

This is 0.010% saponin (100 mg in 1,000 ml of distilled water). This solution should be made fresh as needed.

Apparatus

(a) Centrifuge capable of 3,500 rpm and holding capillary sample tubes.

(b) A pH meter, calibrated to 0.01 pH units.

(c) 0.02 ml Sahli-type hemoglobin pipet.

(d) Constant-temperature bath, 25 C.

(e) 100- and 1,000-ml volumetric flasks.

(f) Heparinized capillary tubes.

(g) A Bunsen burner.

Sampling, Handling, and Preparation

Blood is collected from a clean, dry fingertip in a heparinized glass capillary tube. The blood is allowed to flow into the capillary tube until the tube is approximately 3/4 full, leaving one end free by 1-1.25 inches, to permit flame-sealing of the tip of the tube without overheating the blood sample.

The finger should be pricked deeply and care should be taken to collect only free-flowing drops of blood in order to guard against the initiation of the clotting process before the blood contacts the heparin lining in the wall of the capillary.

One end of the capillary is plugged with solid (room temperature) paraffin and the other (free) end is sealed in the flame of a Bunsen burner. The capillary may now be labeled with an adhesive tape tag bearing a serial number or name and date. The sample should then be centrifuged at 3,000-3,500 rpm for 50-60 minutes. When the sample has been so treated, it may be shipped to a laboratory, if necessary, or stored for several days (preferably in a refrigerator) without appreciable change.

Analysis

For analysis, the capillary is cut cleanly with a sharp ampule file. From the packed-cells section of the capillary,

draw 0.02 ml directly into a Sahli-type hemoglobin pipet. The ends of the capillary must be cut evenly to provide satisfactory juxtaposition with the tip of the pipet. Discharge the contents of the pipet directly into 1.0 ml of 0.01% saponin solution in a microbeaker, and rinse the pipet well (3 times) into the solution. Glass vials, 1 inch (2.5 cm) deep by 3/4 inch (19 mm) in diameter, are convenient for electrometric testing. They will fit in the carrier of a standard pH meter, and, when used with a clean rubber stopper, will eliminate transfer of the sample from a test tube for each pH measurement. Plasma is taken from the appropriate section of the capillary in the same manner as the packed erythrocytes and discharged into 1.0 ml of distilled water, the Sahli pipet being rinsed into the solution (3 times) as with the erythrocytes.

Erythrocyte Cholinesterase Assay

(a) One milliliter of hemolyzed erythrocyte solution is added to 1 ml of buffer solution I and placed in a 25 C water bath.

(b) After a 10-minute equilibrium period, the initial pH(i) is determined to the nearest 0.01 pH unit with the pH meter.

(c) Two-tenths milliliter of 0.11 M acetylcholine chloride solution is added with rapid mixing and the time is recorded.

(d) The reaction proceeds for 1-1.5 hours before the final pH(f) is noted.

The beaker containing the solution should be shaken when the glass electrode is introduced to speed the establishment of equilibrium.

Note: The buffer solution I is designed to yield a pH of 8.00 after the addition of hemolyzed human erythrocytes.

Plasma Cholinesterase Assay

(a) One milliliter of diluted plasma is mixed with 1 ml of buffer solution II.

(b) The solution is allowed to equilibrate in a 25 C water bath for 10 minutes.

(c) At the end of 10 minutes, the initial pH(i) is noted to the nearest 0.01 pH unit.

(d) Two-tenths milliliter of 0.165 M acetylcholine chloride solution is added with rapid mixing.

(e) The reaction mixture is incubated for 1-1.5 hours before the final pH(f) is noted.

Calculations

The final units derived from this assay are Δ pH/hour:

$$\text{Delta pH/hour} = \frac{pH(i) - ph(f) - bc}{t(f) - t(i)}$$

where:

pH(i) = initial pH

pH(f) = final pH

rt(f) - t(i) = time elapsed in hours between reading pH(i) and reading pH(f)

b = nonenzymatic hydrolysis corresponding to pH(f)

c = correction for variations in ΔpH/hour with pH, corresponding to pH(f)

The b and c correction factors are given in Table X-1. Average baseline values of erythrocyte and plasma ChE activity determined by this method for healthy nonexposed men and women are given in Table X-2. The value for average red blood cell (RBC) ChE activity for men is drawn from Wolfsie and Winter. The value for women is obtained by multiplying the average RBC ChE activity figure for men by the ratio of mean Δ pH/hr for women to mean Δ pH/hr for men derived from the data of Rider et al [342]. The use of the data of Wolfsie and Winter [340] allows for the increased packing and possible contamination of RBC's by plasma ChE. Plasma ChE values were selected from Rider et al, since their larger data base probably provides a closer approximation of the true population mean of normal values for plasma ChE activity. For the same reason, their data provide the most reliable women/men ratio for RBC ChE activities. The data of Wolfsie and Winter [340] and Rider et al [342] are presented in Table X-3.

TABLE X-1
CORRECTION FACTORS
FOR USE IN EQUATION FOR Δ pH/HR

pH(f)	Erythrocyte/ Cholinesterase Corrections b	c	Plasma/ Cholinesterase Corrections b	c
7.9	0.03	0.94	0.09	0.98
7.8	0.02	0.95	0.07	1.00
7.7	0.01	0.96	0.06	1.01
7.6	0.00	0.97	0.05	1.02
7.5	0.00	0.98	0.04	1.02
7.4	0.00	0.99	0.03	1.01
7.3	0.00	1.00	0.02	1.01
7.2	0.00	1.00	0.02	1.00
7.1	0.00	1.00	0.02	1.00
7.0	0.00	1.00	0.01	1.00
6.8	0.00	0.99	0.01	1.00
6.6	0.00	0.97	0.01	1.01
6.4	0.00	0.97	0.01	1.02
6.2	0.00	0.97	0.01	1.04
6.0	0.00	0.99	0.01	1.09

Adapted from reference 341

TABLE X-2
MEANS BASELINE VALUES
OF ERYTHROCYTE AND
PLASMA CHOLINESTERASE IN MEN
AND WOMEN (Δ pH/HR)

	Men	Women
	Erythrocyte Cholinesterase	
Mean	0.861	0.843
	Plasma Cholinesterase	
Mean	0.953	0.817

Adapted from Wolfsie and Winter [340] and Rider et al [342]

TABLE X-3
NORMAL VALUES FOR CIRCULATING CHOLINESTERASES
IN HEALTHY NONEXPOSED PERSONS*

Subjects	Erythrocyte Cholinesterase Activity (Δ pH/hr) Range	Mean	SD	Plasma Cholinesterase Activity (Δ pH/hr) Range	Mean	SD	Reference
400 men	0.58-0.95	0.766	0.081	0.52-1.39	0.953	0.187	342**
400 women	0.56-0.94	0.750	0.082	0.38-1.25	0.817	0.187	342**
255 men	0.554-1.252	0.861	0.091	0.408-1.652	0.912	0.112	340***

* All analyses performed by method of Michel [339]
** Ranges, means, and standard deviations in this study are estimates based on data extrapolated to age 40; ranges reflect elimination of highest 1% and lowest 1% of values
*** Analytic method modified for smaller blood sample

XI. APPENDIX III

OSHA EXPOSURE LIMITS FOR CERTAIN PESTICIDES

	ppm	mg/m3
Acrolein	0.1	0.25
Acrylonitrile-Skin* (ETS)	1	
Aldrin-Skin		0.25
Allyl alcohol-Skin	2	5
Ammonia	25	18
ANTU (alpha naphthyl thiourea)		0.3
Azinphos-methyl (Guthion)-Skin		0.2
Barium (soluble compounds)		0.5
Benzene-Skin	2	
Biphenyl	0.2	1
Cadmium		0.2
Calcium arsenate (as As)		1
Camphor, synthetic	2	12
Carbaryl (Sevin)		5
Carbon dioxide	5,000	9,000
Carbon disulfide	20	
Carbon tetrachloride-Skin	10	65
Chlordane-Skin		0.5
Chlorinated camphene (toxaphene)-Skin		0.5
Chlorine	1	3
1-Chloro,2,3-epoxy-propane (epichlorhydrin)	5	20
Chloroform (trichloromethane)	25	120
Chloropicrin	0.1	0.7
Coal tar pitch volatiles		0.2
Copper (dusts and mists)		1
Crag herbicide		10
Chromic acid		0.05
2,4-D (2,4 dichlorophenoxyacetic acid)		10
DBCP (dibromochloropropane)	0.001	
DDT-Skin		1
DDVP (dichlorovos)	0.1	1
Demeton (Systox)-Skin	0.01	0.1
1,2-Dibromoethane (ethylene) dibromide)-Skin	20	145
Dibrom		3
o-Dichlorobenzene	50	300
p-Dichlorobenzene	75	450
1,2-Dichloroethane	50	200

Dichloroethyl ether-Skin	5	30
1,1 Dichloro-1-nitroethane	10	60
1,2 Dichloropropane	75	350
Dieldrin-Skin		0.25
Dimethylphthalate		5
Dinitro-o-cresol-Skin		0.2
Endrin-Skin		0.1
EPN-Skin		0.5
1,2-Epoxypropane (propylene oxide)	100	240
Ethyl acetate	400	1,400
Ethyl formate	100	300
Ferbam		10
Formaldehyde	2	3
Furfural-Skin	5	20
Heptachlor-Skin		0.5
Hydrogen cyanide-Skin	10	11
Hydrogen fluoride	3	
Isopropyl alcohol	400	980
Lead arsenate (as PB)		0.15
Lindane-Skin		0.5
Malathion-Skin		15
Mercury		0.1
Methoxychlor		10
Methyl alcohol	200	260
Methyl bromide-Skin	15	60
Methyl chloride	100	210
Methyl chloroform	350	1,900
Methylene chloride	200	720
Napathalene	10	50
Nickel, soluble compounds (as Ni)		0.1
Nicotine-Skin		0.5
Nitrobenzene-Skin	1	5
Paraquat-Skin		0.5
Parathion-Skin		0.1
Pentachlorophenol-Skin		0.5
Pentane	600	1,800
Perchloroethylene-Skin	100	670
Petroleum distillates (naphtha)	500	2,000
Phenol-Skin	5	19
Phosdrin (mevinphos)-Skin	0.01	0.1
Phosphine	0.3	0.4
Pival (2-pivalyl-1, 3-indandione)		0.1
Propargyl alcohol-Skin	1	2
Propylene dichloride (1,2 dichloropropane)	75	350
Pyrethrum		5
Pyridine	5	15
Ronnel		10
Rotenone (commercial)		5
Silica, crystalline (respirable free silica)		0.05

	ppm	mg/m3
Sodium fluoroacetate (1080)-Skin	100	575
Stoddard solvent	500	2,950
Strychnine		0.15
Sulfuric acid		1
2,4,5-T		10
TEDP-Skin		0.2
TEPP-Skin	0.004	0.05
1,1,2,2-Tetrachloroethane-Skin	5	35
Thiram		5
Tin (organic)		0.1
Trichloroethylene	100	535
Warfarin		0.1
Xylene	100	435
Zinc chloride fume		1

Adapted from 29 CFR 1910.1000
*Standards denoted "Skin" apply to both dermal and respiratory exposure

XII. APPENDIX IV

NIOSH RECOMMENDED EXPOSURE LIMITS FOR CERTAIN PESTICIDES

Substance	NIOSH Recommendations For Workplace Air Exposure Limits
Acrylonitrile	4 ppm ceiling (4 hrs)
Arsenic, Inorganic	2 μg(As)/m3 ceiling[a] (15-minute)
Benzene	1 ppm ceiling (120-minute)
Cadmium	40 μg(Cd)/m3 TWA; 200 μg(Cd)/m3 ceiling(15-minute)
Carbaryl	5 mg/m3 TWA
Carbon dioxide	10,000 ppm TWA; 30,000 ppm ceiling (10-minute)
Carbon disulfide	3 mg/m3 TWA 30 mg/m3 ceiling (15-minute)
Carbon tetrachloride	2 ppm, ceiling (60-minute)
Chlorine	0.5 ppm ceiling (15 minute)
Chloroform	2 ppm ceiling (60-minute)
Chromic acid	0.05 mg(CrO3)/m3 TWA 0.1 mg (CrO3)/m3 ceiling (15-minute)
Creosote[b]	0.1 mg/m3 TWA

Cyanide Salts and Hydrogen Cyanide	5 mg(CN)/m3 ceiling (10-minute)
1,2-Dibromo-3-Chloropropane	10 ppb TWA
Epichlorohydrin	2 mg/m3 TWA 19 mg/m3 ceiling (15-minute)
Ethylene dichloride	5 ppm TWA; 15 ppm ceiling (15-minute)
Formaldehyde	1.2 mg/m3 ceiling (30-minute)
Hydrogen fluoride	2.5 mg (F)/m3 TWA; 5.0 mg/m3 ceiling (15-minute,fluoride ion)
Kepone	1 μg/m3 ceiling (15-minute)
Lead, Inorganic[c]	<100 μg/m3
Malathion	15 mg/m3 TWA
Mercury, Inorganic	0.05 mg/m3 TWA
Methyl alcohol	200 ppm TWA; 800 ppm ceiling (15-minute)
Methyl parathion	0.2 mg/m3 TWA
Methylene chloride	75 ppm TWA; 500 ppm ceiling, (15-minute). TWA to be lowered in presence of carbon monoxide
Nickel, Inorganic	15 μg/m3 TWA
Organotin compounds	0.1 mg(tin)/m3 TWA
Parathion	0.05 mg/m3 TWA
Pentane[d]	350 mg/m3 TWA 1,800 mg/m3 ceiling

	(15-minute)
Phenol	20 mg/m3 TWA 60 mg/m3 ceiling (15-minute)
Mineral spirits,[e] Kerosene, Stoddard solvent	350 mg/m3 TWA 1,800 mg/m3 ceiling (15-minute)
Silica, Crystalline	50 μg/m3 TWA respirable free silica
Sulfur dioxide	2 ppm TWA
Sulfuric acid	1 mg/m3 TWA
1,1,2,2-Tetrachloroethane	1 ppm TWA
Toluene	100 ppm TWA; 200 ppm ceiling (10-minute)
Trichloroethylene[f]	< 25 ppm TWA
Xylene	100 ppm TWA; 200 ppm ceiling (10-minute)
Zinc oxide	5 mg/m3 TWA; 15 mg/m3 ceiling (15-minute)

Adapted from reference 153

a NIOSH TWA recommendations based on up to a 10-hr/d, 40-hr/wk exposure unless otherwise noted
b Recommended in the Coal Tar Products Criteria Document
c Revised, March 1977 in NIOSH testimony at OSHA hearings
d Recommended in the Alkanes Criteria Document
e Recommended in the Refined Petroleum Solvents Criteria Document
f Revised, January 1978 in Special Occupational Hazard Review on Trichloroethylene

XIII. APPENDIX V

MATERIAL SAFETY DATA SHEET

General instructions for preparing a Material Safety Data Sheet (MSDS) are presented in this chapter. The examples used in this text are for illustrative purposes and are not intended to apply to any specific compound or product. Applicable information about a specific product or material shall be supplied in the appropriate block of the MSDS.

The product designation is inserted in the block in the upper left corner of the first page to facilitate filing and retrieval. Print in upper case letters as large as possible. It should be printed to read upright with the sheet turned sideways. The product designation is that name or code designation which appears on the label, or by which the product is sold or known to employees. The relative numerical hazard ratings and key statements are those determined by the guidelines in Chapter V, Part B, of the NIOSH publication, An Identification System for Occupationally Hazardous Materials. The company identification may be printed in the upper right corner if desired.

(a) Section I. Product Identification

The manufacturer's name, address, and regular and emergency telephone numbers (including area code) are inserted in the appropriate blocks of Section I. The company listed should be a source of detailed backup information on the hazards of the

material(s) covered by the MSDS. The listing of suppliers or wholesale distributors is discouraged. The trade name should be the product designation or common name associated with the material. The synonyms are those commonly used for the product, especially formal chemical nomenclature. Every known chemical designation or competitor's trade name need not be listed.

(b) Section II. Hazardous Ingredients

The "materials" listed in Section II should be those substances which are part of the hazardous product covered by the MSDS and which individually meet any of the criteria defining a hazardous material. Thus, one component of a mulitcomponent product might be listed because of its toxicity, another component because of its flammability, while a third component could be included both for its toxicity and its reactivity. Note that a MSDS for a single component product must have the name of the material repeated in this section to avoid giving the impression that there are no hazardous ingredients.

Chemical substances should be listed according to their complete name derived from a recognized system of nomenclature. Where possible, avoid using common names and general class names such as "aromatic amine," "safety solvent," or "aliphatic hydrocarbon" when the specific name is known.

The "%" may be the approximate percentage by weight or volume (indicate basis) which each hazardous ingredient of the mixture bears to the whole mixture. This may be indicated as a range or maximum amount, ie, "10-40% vol" or "10% max wt," to avoid disclosure of trade secrets.

Toxic hazard data should be stated in terms of concentration, mode of exposure or test, and animal used, eg, "100 ppm LC50-rat," "25 mg/kg LD50-skin-rabbit," "75 ppm LC man," or "permissible exposure from 29 CFR 1910.1000" or, if not available, from other sources or publications such as the American Conference of Governmental Industrial Hygienists or the American National Standards Institute, Inc. Flashpoint, shock sensitivity, or similar descriptive data may be used to indicate flammability, reactivity, or similar hazardous properties of the material.

(c) Section III. Physical Data

The data in Section III should be for the total mixture and should include the boiling and melting points in degrees Fahrenheit (Celsius in parentheses); vapor pressure, in conventional millimeters of mercury (mm Hg); vapor density of gas or vapor (air=1); solubility in water, in parts/hundred parts of water by weight; specific gravity (water=1); percent volatiles (indicate if by weight or volume) at 70 F (21.1 C);

evaporation rate for liquids or sublimable solids, relative to butyl acetate; and appearance and odor. These data are useful for the control of toxic substances. Boiling point, vapor density, percent volatiles, vapor pressure, and evaporation are useful for designing proper ventilation equipment. This information is also useful for design and deployment of adequate fire and spill containment equipment. The appearance and odor may facilitate identification of substances stored in improperly marked containers, or when substances are spilled.

(d) Section IV. Fire and Explosion Data

Section IV should contain complete fire and explosion data for the product, including flashpoint and autoignition temperature in degrees Fahrenheit (Celsius in parentheses); flammable limits, in percent by volume in air; suitable extinguishing media or materials; special firefighting procedures; and unusual fire and explosion hazard information. If the product presents no fire hazard, insert "NO FIRE HAZARD" on the line labeled "Extinguishing Media."

(e) Section V. Health Hazard Information

The "Health Hazard Data" should be a combined estimate of the hazard of the total product. This can be expressed as a TWA concentration, as a permissible exposure, or by some other indication of an acceptable limit. Other data are acceptable, such as lowest LD50, if multiple components are involved.

Under "Routes of Exposure," comments in each category should reflect the potential hazard from absorption by the route in question. Comments should indicate the severity of the effect and the basis for the statement, if possible. The basis might be animal studies, analogy with similar products, or human experiences. Comments such as "yes" or "possible" are not helpful. Typical comments might be:

Skin Contact--single short contact, no adverse effects likely; prolonged or repeated contact, irritation, and cracking. Readily absorbed through the skin with severe systemic effects.

Eye Contact--some pain and mild transient irritation;

no corneal scarring.

"Emergency and First Aid Procedures" should be written in lay language and should primarily represent first-aid treatment that should be provided by paramedical personnel or individuals trained in first aid.

Information in the "Notes to Physician" section should include any special medical information which would be of assistance to an attending physician including required or recommended preplacement and periodic medical examinations, diagnostic procedures, and medical management of overexposed employees.

(f) Section VI. Reactivity Data

The comments in Section VI relate to safe storage and handling of hazardous, unstable substances. It is particularly important to highlight instability or incompatibility to common substances or circumstances such as water, direct sunlight, steel or copper piping, acids, alkalies, etc. "Hazardous Decomposition Products" should include those products released under fire conditions. It must also include dangerous products produced by aging, such as peroxides in the case of some ethers. Where applicable, shelf life should also be indicated.

(g) Section VII. Spill or Leak Procedures

Detailed procedures for cleanup and disposal should be listed with emphasis on precautions to be taken to protect workers assigned to cleanup detail. Specific neutralizing chemicals or procedures should be described in detail. Disposal methods should be explicit and should include proper labeling of

containers holding residues and ultimate disposal methods such as "sanitary landfill" or "incineration." Warnings such as "comply with local, state, and Federal anti-pollution ordinances" are proper but not sufficient. Specific procedures should be identified.

(h) Section VIII. Special Protection Information

Section VIII requires specific information. Statements such as "Yes," "No," or "If Necessary" are not informative. Ventilation requirements should be specific as to type and preferred methods. Specify respirators as to type and NIOSH or US Bureau of Mines approval class, ie, "Supplied air," "Organic vapor canister," "Suitable for dusts not more toxic than lead," etc. Protective equipment must be specified as to type and materials of construction.

(i) Section IX. Special Precautions

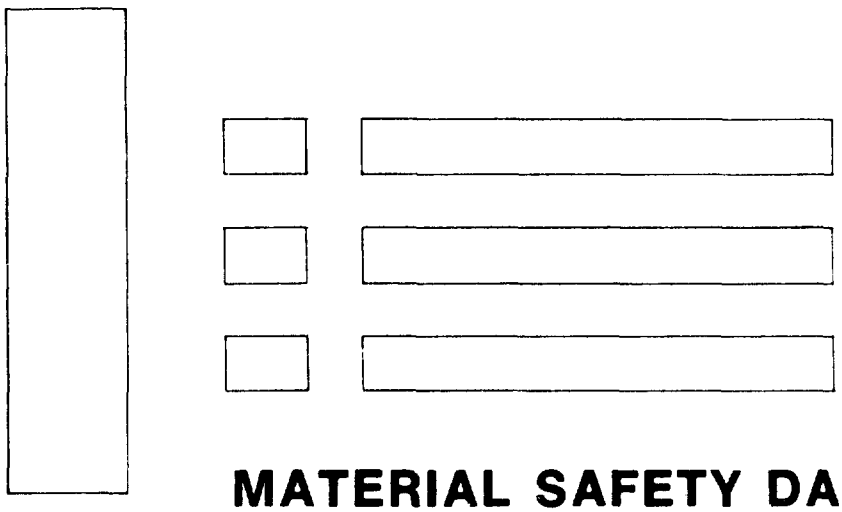
"Precautionary Statements" should consist of the label statements selected for use on the container or placard. Additional information on any aspect of safety or health not covered in other sections should be inserted in Section IX. The lower block can contain references to published guides or in-house procedures for handling and storage. Department of Transportation markings and classifications, other freight, handling, or storage requirements, and environmental controls can be noted.

(j) Signature and Filing

Finally, the name and address of the responsible person who completed the MSDS and the date of completion are entered. This

will facilitate correction of errors and identify a source of additional information.

The MSDS shall be filed in a location readily accessible to workers potentially exposed to the hazardous material. The MSDS can be used as a training aid and as a basis for discussion during safety meetings and training of new employees. It should assist management by directing attention to the need for specific control engineering, work practices, and protective measures to ensure safe handling and use of the material. It will aid the safety and health staff in planning a safe and healthful work environment and in suggesting appropriate emergency procedures and sources of help in the event of harmful exposure of employees.



MATERIAL SAFETY DATA SHEET

I PRODUCT IDENTIFICATION	
MANUFACTURER'S NAME	REGULAR TELEPHONE NO EMERGENCY TELEPHONE NO
ADDRESS	
TRADE NAME	
SYNONYMS	

II HAZARDOUS INGREDIENTS		
MATERIAL OR COMPONENT	%	HAZARD DATA

III PHYSICAL DATA		
BOILING POINT, 760 MM HG		MELTING POINT
SPECIFIC GRAVITY (H_2O=1)		VAPOR PRESSURE
VAPOR DENSITY (AIR=1)		SOLUBILITY IN H_2O, % BY WT
% VOLATILES BY VOL		EVAPORATION RATE (BUTYL ACETATE=1)
APPEARANCE AND ODOR		

IV FIRE AND EXPLOSION DATA

FLASH POINT (TEST METHOD)		AUTOIGNITION TEMPERATURE	
FLAMMABLE LIMITS IN AIR, % BY VOL.	LOWER		UPPER
EXTINGUISHING MEDIA			
SPECIAL FIRE FIGHTING PROCEDURES			
UNUSUAL FIRE AND EXPLOSION HAZARD			

V HEALTH HAZARD INFORMATION

HEALTH HAZARD DATA

ROUTES OF EXPOSURE

INHALATION

SKIN CONTACT

SKIN ABSORPTION

EYE CONTACT

INGESTION

EFFECTS OF OVEREXPOSURE

ACUTE OVEREXPOSURE

CHRONIC OVEREXPOSURE

EMERGENCY AND FIRST AID PROCEDURES

EYES

SKIN

INHALATION

INGESTION

NOTES TO PHYSICIAN

VI REACTIVITY DATA

CONDITIONS CONTRIBUTING TO INSTABILITY

INCOMPATIBILITY

HAZARDOUS DECOMPOSITION PRODUCTS

CONDITIONS CONTRIBUTING TO HAZARDOUS POLYMERIZATION

VII SPILL OR LEAK PROCEDURES

STEPS TO BE TAKEN IF MATERIAL IS RELEASED OR SPILLED

NEUTRALIZING CHEMICALS

WASTE DISPOSAL METHOD

VIII SPECIAL PROTECTION INFORMATION

VENTILATION REQUIREMENTS

SPECIFIC PERSONAL PROTECTIVE EQUIPMENT

RESPIRATORY (SPECIFY IN DETAIL)

EYE

GLOVES

OTHER CLOTHING AND EQUIPMENT

IX SPECIAL PRECAUTIONS

PRECAUTIONARY
STATEMENTS

OTHER HANDLING AND
STORAGE REQUIREMENTS

PREPARED BY _____

ADDRESS _____

DATE _____

TABLE XIV-1

PRODUCTION AND USE OF MAJOR PESTICIDES, 1975 ESTIMATES

Production (Range in Millions of Pounds Per Year)	Name of Pesticide	Use
>200	Creosote	Fungicide or wood preservative
100-200	Atrazine	Herbicide
	Coal tars	Fungicide or wood perservative
	Inorganic sulfurs	"
50-99	Toxaphene	Insecticide
	Carbaryl	"
	Pentachlorophenol	Fungicide or wood preservative
	Dichlorobenzene	Fumigant
30-49	DDT	Insecticide
	Methyl parathion	"
	Malathion	"
	2,4-D	Herbicide
	Inorganic coppers	Fungicide or wood preservative
15-29	Chlordane	Insecticide
	Parathion	"
	Propachlor	Herbicide
	Alachlor	"
	Chloramben (Amiben)	"
	Trifluralin	"
	MSMA	"
	Trichlorophenol	Fungicide or wood preservative
	Captan	"
	Methyl bromide	Fumigant
	Ethylene dibromide	"
5-14	Aldrin	Insecticide
	Methoxychlor	"
	Heptachlor	"
	Diazinon	"
	Disulfoton	"
	Phorate	"
	Monocrotophos	"
	Chlorpyrifos	"
	Simazine	Herbicide
	CDAA	"

TABLE XIV-1 (CONTINUED)

PRODUCTION AND USE OF MAJOR PESTICIDES, 1975 ESTIMATES

Production (Range in Millions of Pounds Per Year)	Name of Pesticide	Use
5-14	Propanil	Herbicide
	2,4,5-T	"
	DSMA	"
	Bromacil	"
	Diuron	"
	Butylate	"
	EPTC	"
	TCA	"
	DEF	"
	Chromates	Fungicide or wood preservative
	Maneb	"
	Methane	"
	Benomyl	"
	Carbon tetrachloride	Fumigant
	Ethylene dichloride	"
	Naphthalene	"

Adapted from reference 7

TABLE XIV-2

PESTICIDE INDUSTRY STATISTICS, 1972

Type of Establishment	Number of Establishments	Pesticide Value of Shipment (Millions of Dollars)
Primary pesticide production		
Manufacturing (SIC 2869)	19	489.3
Formulating (SIC 2879)	388	867.0
Northeast	56	
North Central	89	
South	161	
West	82	
Subtotal (SIC's 2869, 2879)	407	1,356.3
Other establishments where pesticide manufacturing and formulation is a secondary industry (eg, SIC's 2842, 2821, 2834, 2819)	6,679	329.2
Total (all SIC's)	7,086	1,685.5

Adapted from reference 9

TABLE XIV-3

GEOGRAPHIC DISTRIBUTION OF TOTAL VALUE SHIPMENT, 1972

Region	Manufacturing		Formulating		Total	
	Value of Shipment ($Million)	Percent of Total	Value of Shipment ($Million)	Percent of Total	Value of Shipment ($Million)	Percent of Total
Northeast	60.9	12	140.0	11	200.9	12
North Central	195.9	40	439.0	37	634.9	38
South	219.5	45	488.0	41	707.5	42
West	13.0	3	129.2	11	142.2	8
TOTAL	489.3	100	1,196.2	100	1,685.5	100

Adapted from reference 9

TABLE XIV-4

WORKERS POTENTIALLY EXPOSED IN THE
MANUFACTURE AND FORMULATION OF PESTICIDES, 1972

Type of Establishment	Number of Establishments	Number of Production Workers
Manufacturing (SIC 2869)	19	1,900
Formulation (SIC 2879)	388	6,800
Total (SIC 2869, 2879)	407	8,700
Other establishments where pesticide manufacturing and formulation is a secondary activity (eg, SIC's 2842, 2821, 2834, 2819)	6,679	355,300
Total (all SIC's)	7,086	364,000

Adapted from reference 9

TABLE XIV-5
DISTRIBUTION OF FORMULATION PLANT WORKERS

Size of Plant (Number of Employees)	Number of Plant Production Workers
1-19	1,000
20-95	2,100
100-499	1,600
>500	2,100
Total	6,800

Adapted from reference 9

TABLE XIV-6

PESTICIDE MASS POISIONINGS

Kind of Accident	Pesticide Involved	Material Contaminated	Number Affected	Number Died	Location
Spillage during transport or storage	Endrin	Flour	159	0	Wales
	"	"	691	24	Qatar
	"	"	183	2	Saudi Arabia
	Dieldrin	Food	20	0	Shipboard
	Diazinon	Doughnut mix	20	0	USA
	Parathion	Wheat	360	102	India
	"	Barley	38	9	Malaya
	"	Flour	200	8	Egypt
	"	"	600	88	Columbia
	"	Sugar	300	17	Mexico
	"	Sheets	3	0	Canada
	Mevinphos	Plants	6	0	USA
Accidental ingestions	Hexachlorobenzene	Seed grain	>3,000	3-11%	Turkey
	Organic mercury	"	34	4	West Pakistan
	"	"	321	35	Iraq
	"	"	45	20	Guatemala
	Warfarin	Bait	14	2	Korea
Improper use	Toxaphene	Collards and chard	7	0	USA
	Nicotine	Mustard	11	0	USA
	Parathion	Used as treatment for body lice	>17	15	Iran
	Pentachlorophenol	Nursery linens	20	2	USA

Adapted from reference 73

TABLE XIV-7

REPORTS OF OCCUPATIONAL DISEASE ATTRIBUTED TO PESTICIDES AND OTHER AGRICULTURAL CHEMICALS IN CALIFORNIA, 1973

Agricultural Chemical	Total	Agriculture	Manufacturing	Construction	Transportation, Communication & Utilities	Trade	Structural Pest Control	State & Local Government	Other and Unspecified
TOTAL	1,451	887	156	39	53	65	34	157	60
Organophosphorus Pesticides	260	182	32	--	9	10	7	14	6
Parathion	53	43	5	--	1	2	--	1	1
Systox	9	8	--	--	--	--	--	1	--
TEPP	3	2	--	--	--	1	--	--	--
Phosdrin	14	11	2	--	--	1	--	--	--
Malathion	13	6	1	--	1	1	--	2	2
Trithion	2	1	1	--	1	--	--	--	--
Thimet	2	2	--	--	--	--	--	--	--
Guthion	4	2	--	--	1	--	--	--	1
Other and unspecified	160	107	24	--	5	5	7	10	2
Halogenated Hydrocarbon Pesticides	105	44	20	--	4	5	11	17	4
Chlordane, lindane, kelthane	22	4	6	--	1	3	4	1	3
Endrin, aldrin, dieldrin, toxaphene	2	--	--	--	--	1	1	--	--
Methyl bromide	32	8	11	--	--	1	2	9	1
Other and unspecified	49	32	3	--	3	--	4	7	--
Lead and/or Arsenic Compounds	7	2	2	--	1	--	--	2	--
Herbicides (defoliants and weed killers)	208	96	14	4	12	12	--	53	17
Fertilizers	194	140	26	--	2	11	--	5	10
Organo-Mercury Compounds	5	--	5	--	--	--	--	--	--
Fungicides, Not Elsewhere Classified	55	25	8	11	7	1	--	--	3
Phenolic Compounds	57	12	13	15	6	1	3	4	3
Carbamates	37	36	--	--	--	1	--	--	--
Sulfur	50	43	2	--	2	1	1	1	--
Other Specified Agriculture Chemicals	70	16	13	--	2	6	4	26	3
Unspecified	403	291	21	9	8	17	8	35	14

Adapted from reference 17

TABLE XIV-8

SUSPECTED OCCUPATIONAL CARCINOGENS

Pesticide	Author, Ref	Species (Strain)	Sex	Dose and Route	Cancer Site	Statistical Significance
Aldrin/ Dieldrin	NIOSH, 2	(Numerous reports in literature)				
Bis (2-chloro-ethyl) ether	NCI, Bionetics, 4	Mouse (B6C3F1, B6AKF1)	M,F	100 mg/kg/d, 21 d oral, then 300 mg/kg/ diet	Liver	P=0.01
			M,F	215 mg/kg sc on d 28	Reticulum cell	P=0.01
Bis (2-hydroxy-ethyl)-dithiocar-bamic acid, potassium salt	NCI, Bionetics, 4	"	M,F	464 mg/kg/d, 21 d oral, then 1,112 ppm/diet	Liver	P=0.01
Ethylenebis-dithiocarbamic acid salts	Inference from Ethylene thiourea					
2-(p-tert-butyl-phenoxy)-isopro-pyl-2-chloroethyl sulfite	NCI, Bionetics, 4	"	M	464 mg/kg/d, 21 d oral, then 1,112 ppm/diet	Liver	P=0.05
	Oser and Oser, 194	Rat (FDRL)	M,F	400 ppm/diet	Liver, bile duct	
	Sternberg et al, 195	Dog (mongrel)	M,F	500 or 828-1,420 ppm/diet	Biliary system	
Captan	NCI, 197	Rat (Osborne-Mendel)	M,F	2,525 or 6,050 ppm/ diet	Adrenal gland, thyroid	P=0.047 P=0.035
		Mouse (B6C3F1)	M	8,000 or 16,000 ppm/ diet	Duodenum	P=0.008
		"	F	8,000 or 16,000 ppm/ diet	"	P=0.022
Carbon tetrachloride	Reuber and Glover, 198	Rat (Osborne-Mendel; Japanese)	M	1.3 ml/kg of 50% solution 2x/wk, sc	Liver	
	Della Porter et al, 200	Hamster (Syrian)	M,F	0.0625-0.125 ml/kg, oral	"	

TABLE XIV-8 (CONTINUED)

SUSPECTED OCCUPATIONAL CARCINOGENS

Pesticide	Author, Ref	Species (Strain)	Sex	Dose and Route	Cancer Site	Statistical Significance
Chloramben	NCI, 202	Mouse (B6C3F1)	F	10,000 or 20,000 ppm/diet	Liver	P<0.004
			M	10,000 or 20,000 ppm/diet	"	(P<0.029)
Chlordane	NCI, 203	"	M	158.9 or 56.2 ppm/ diet	"	P<0.001
			F	30.1 or 63.8 ppm/ diet	"	P<0.0001
		Rat (Osborne-Mendel)	M	158.9 or 56.2 ppm/ diet	Negative	
			F	30.1 or 63.8 ppm/ diet		
Chlorobenzilate	NCI, Bionetics, 4	Mouse (B6C3F1, B6AKF1)	M,F	215 mg/kg/d, 21 d oral, then 603 ppm/ diet	Liver	P=0.01
	NCI, 204	Mouse (B6C3F1)	M,F	3,200-7,846 ppm, diet	"	P=0.001
Chloroform	NCI,199	Mouse (B6C3F1)	M	138 or 277 mg/kg/ 5x/wk, oral	Liver	P<0.001
			F	238 or 477 mg/kg/ 5x/wk, oral	"	P<0.001
		Rat (Osborne-Mendel)	M	90 and 180 mg/kg, oral	Kidney	P=0.0016
DBCP	NCI, 206	Mouse (B6C3F1)	M	113 or 219 mg/kg/d 5x/wk, oral	Stomach	
		Rat (Osborne-Mendel)	F	109 or 209 mg/kg/d 5x/wk, oral	"	
		"	F	15 or 29 mg/kg/d 5x/wk, oral	Mammaries, stomach	
DDT	NIOSH, 31	(Numerous reports in literature)				
p,p'-DDD	"	"		"		
o,p'-DDD	"	"		"		

TABLE XIV-8 (CONTINUED)

SUSPECTED OCCUPATIONAL CARCINOGENS

Pesticide	Author, Ref	Species (Strain)	Sex	Dose and Route	Cancer Site	Statistical Significance
EDB	Powers et al, 209, 210	Mouse (B6C3F1)	M,F	60 or 120 mg/kg/d 5x/wk, oral	Stomach	
		Rat (Osborne-Mendel)	M,F	40 or 80 mg/kg/d 5x/wk, oral	"	
Heptachlor	NCI, 211	Mouse (B6C3F1)	M	6.1-18 ppm/diet	Liver	P=0.001
			F	9-18 ppm/diet	"	P<0.001
		Rat (Osborne-Mendel)	M	38.9-77.9 ppm/diet	Negative	
			F	25.7-51.3 ppm/diet	"	
Kepone	NCI, 85	Mouse (B6C3F1)	M	20-23 ppm/diet	Liver	P<0.05
			F	20-40 ppm/diet	"	P<0.05
		Rat (Osborne-Mendel)	M	8-24 ppm/diet	"	P<0.05
			F	8-26 ppm/diet	"	P<0.05
Mirex	NCI, Bionetics, 4	Mouse (B6C3F1, B6AKF1)	M,F	10 mg/kg/d, 21 d oral, then 26 ppm/diet	Liver	P=0.01
			M,F	1,000 mg/kg sc on d 28	Liver, reticulum cells	P=0.01
	Ulland et al, 5	Rat (Charles River CD)	M,F	50 and 100 ppm/diet	Liver	
Nitrofen	NCI, 213	Rat (Osborne-Mendel)	F	1,300 or 2,600 ppm/ diet	Pancreas	P<0.001
		Mouse (B6C3F1)	M,F	2,348 or 4,696 ppm/ diet	Liver, hemangiosarcoma of liver	P<0.001 P=0.022 (high-dose male)

TABLE XIV-8 (CONTINUED)

SUSPECTED OCCUPATIONAL CARCINOGENS

Pesticide	Author, Ref	Species (Strain)	Sex	Dose and Route	Cancer Site	Statistical Significance
2-Nitropropane	NIOSH, 214	Rat (Sprague-Dawley)	M	207 ppm/d 5x/wk inhalation	Negative	
		Rat		300 ppm/119 hr, inhalation	Clear cell foci	
		Cat		328 ppm inhalation	Negative	
1,1,2,2-Tetrachloroethane	NCI, 215	Mouse (B6C3F1)	M,F	142 or 282 mg/kg/d, gavage	Liver	P<0.001
Tetrachloroethylene	NCI, 216	"	F	386 or 772 mg/kg/d, gavage	"	P<0.001
			M	536 or 1,072 mg/kg/d, gavage	"	P<0.001
Tetrachlorvinphos	NCI, 217	"	M	8,000 or 16,000 ppm/diet	"	P<0.001
		"	F	8,000 or 16,000 ppm/diet	Neoplastic nodule	P=0.007
		Rat (Osborne-Mendel)	F	4,250 or 8,500 ppm/diet	Thyroid, adrenal	P=0.013, P=0.017
Trichloroethylene	NCI, 218	Mouse (B6C3F1)	M	2,339 mg/kg/d, 5x/wk oral or	Liver	P<0.001
				1,169 mg/kg/d, 5x/wk oral	"	P=0.004
			F	1,739 mg/kg/d, 5x/wk oral	"	P=0.008
Trifluralin	NCI, 220	"	F	2,740 or 5,192 ppm/diet	Liver	P<0.001
					Lung, stomach	P<0.036 Not significant

TABLE XIV-9

EXAMPLES OF PESTICIDES CONSIDERED BY NIOSH TO REQUIRE FURTHER CARCINOGENICITY TESTING

Pesticide	Author, Ref	Species (Strain)	Sex	Dose and Route	Cancer Site	Statistical Significance
Azobenzene	NCI, Bionetics, 4	Mouse (B6C3F1, B6AKF1)	M	21.5 mg/kg/d,21 d oral then 56 mg/kg/ diet	Site of Injection	P=0.01
			M,F	1,000 mg/kg sc on d 28	Negative	
Calcium cyanamide	"	Mouse (B6C3F1,B6AKF1)	M,F	100 mg/kg/d, 21 d oral, then 240 ppm/ diet	Reticulum Cell	P=0.01
(2-chloroethyl) triethylammonium chloride (CCC)	"	"	M,F	21.5 mg/kg/d, 21 d oral, then 65 ppm/ diet	Liver	P=0.01
Chloropicrin	NCI, 221	Mouse (B6C3F1)	M	66 mg/kg/d, gavage	Carcinoma, papilloma	Not statistically significant
CIPC	van Esch et al, 239	Mouse (Swiss)	F	15 mg single dose, oral	Papillomas	P<0.05
2,4-D	Hansen et al, 222	Rat (Osborne-Mendel)	M	1,250 mg/kg/diet	Various	P<0.05
	Arkhipov and Koslova, 223	Rat		Diet	Negative	
	NCI, Bionetics, 4	Mouse (B6C3F1, B6AKF1)	M,F	149 and 323 ppm/diet, 215 and 464 mg/kg injection	"	
		"	M,F	21.5 mg isooctyl ester/kg sc on d 7	Reticulum cells	P=0.01
Dimethoate	NCI, 225	Rat (Osborne-Mendel)	M,F	155-500 ppm/diet	Negative	
		Mouse (B6C3F1)	M,F	155-500 ppm/diet	"	
	Gibel et al, 224	Rat (Wistar)	M,F	5-30 mg/kg/d, oral	Spleen, liver various	
		"	M,F	15 mg/kg/d, im	Spleen, various	
		Mouse (AB)	M,F	Topical	Leukosis	

TABLE XIV-9 (CONTINUED)

EXAMPLES OF PESTICIDES CONSIDERED BY NIOSH TO REQUIRE FURTHER CARCINOGENICITY TESTING

Pesticide	Author, Ref	Species (Strain)	Sex	Dose and Route	Cancer Site	Statistical Significance
Dimethoxane	Hoch-Ligeti et al, 226	Rat (Wistar)	M *	1% solution in drinking water	Liver	
2,4-Dinitrotoluene	NCI, 227	Rat (Fischer 344)	M,F	0.008% and 0.02%, diet	Benign fibroma, benign mammary fibroadenoma	P=0.003 P=0.016
Diphenyl acetonitrile	NCI, Bionetics, 4	Mouse (B6C3F1, B6AKF1)	M,F	464 mg/kg sc on d 28	Reticulum cell	P=0.01
Endosulfan	"	Mouse (B6C3F1, B6AKF1)	M,F	1.0 mg/kg/d/21 d oral, then 3 ppm/diet	Lung	P=0.05
	NCI, 228	Mouse (B6C3F1)	M,F	2.0-6.9 ppm, diet	Negative, early mortality	
		Rat (Osborne-Mendel)	M,F	223-952 ppm, diet	"	
Endrin	Treon et al, 229	Rat (Carworth)	M,F	1,5,25,50 or 100 ppm/ diet	Negative	
	Deichmann et al, 230	Rat (Osborne-Mendel)	M,F	2,6 or 12 ppm/diet	"	
Ethylan	NCI, Bionetics, 4	Mouse (B6C3F1, B6AKF1)	M,F	215 mg/kg/d, 21 d oral, then 815 ppm/ diet	Liver	P=0.01
Ethylene oxide	Reyniers et al, 231	Mouse (ALBM-2)	F	Bedding	Various	
	Van Duuren, 232	Mouse (Swiss-Millerton)	F	0.1 ml of 10% solution 3x/wk,skin painting	Negative	
	Walpole, 233	Rat (Wistar)		1 g/kg sc	"	

TABLE XIV-9 (CONTINUED)

EXAMPLES OF PESTICIDES CONSIDERED BY NIOSH TO REQUIRE FURTHER CARCINOGENICITY TESTING

Pesticide	Author, Ref	Species (Strain)	Sex	Dose and Route	Cancer Site	Statistical Significance
HCCH	Nagasaki et al, 235,236	Mouse (dd)	M	600 ppm/diet	Liver	
	Goto et al, 237	Mouse (ICR-JCL)	M	600 ppm/diet	Liver nodules	
	Fitzhugh et al, 238	Rat (Wistar)	M,F	10-800 ppm/diet	Negative	
IPC	van Esch et al, 239	Mouse (Swiss)	M,F	15 mg/wk 10 wk oral	Papillomas	P<0.05
Lindane	NCI, 240	Mouse (B6C3F1)	M	80 ppm/diet	Liver	P=0.001
		"	M,F	80 ppm (female mice)-472 ppm/diet	Negative	
		Rat (Osborne-Mendel)	M,F	80 ppm (female mice)-472 ppm/diet	"	
	Nagasaki et al, 241	Mouse (dd)	M	100/500 ppm/diet	"	
	Fitzhugh et al, 238	Rat (Wistar)	M,F	5-1,600 ppm/diet	"	
	Thorpe and Walker, 242	Mouse (CF1)	M,F	400 ppm/diet	Liver	
	Goto et al, 237	Mouse (ICR-JCL)	M	300 ppm/diet	Liver nodules	
Mexacarbate	NCI, Bionetics, 4	Mouse (B6C3F1, B6AKF1)	M,F	4.64 mg/kg/d, 21 d oral, then 11 ppm/diet	Liver	P=0.05
PCNB	"	"	M,F	464 mg/kg/d 21 d oral, then 1,206 ppm/diet	"	P=0.01
	NCI, 243	Mouse (B6C3F1)	M,F	14,635 ppm/diet	Negative	
		Rat (Osborne-Mendel)	M,F			

TABLE XIV-9 (CONTINUED)

EXAMPLES OF PESTICIDES CONSIDERED BY NIOSH TO REQUIRE FURTHER CARCINOGENICITY TESTING

Pesticide	Author, Ref	Species (Strain)	Sex	Dose and Route	Cancer Site	Statistical Significance
Piperonyl butoxide	NCI, Bionetics, 4	Mouse (B6C3F1, B6AKF1)	M,F	100 mg/kg/d, 21 d oral, then 300 ppm/ diet	Reticulum cell	P=0.05
Piperonyl sulfoxide	"	"	M,F	46.4 mg/kg/ sc injection	"	P=0.05
			M,F	46.4 mg/kg/d, 21 d oral, then 111 ppm/ diet	"	P=0.01
Sodium N,N-dimethyl dithiocarbamate (SDDC)	"	"	M,F	215 mg/kg/d, 21 d oral, then 692 ppm/ diet	"	P=0.05
Strobane	"	"	M	4.64 mg/kg/d, 21 d oral then 11 ppm/diet	"	P=0.01
			M,F	4.64 mg/kg/d, 21 d oral then 11 ppm/diet	Reticulum cells	P=0.05
2,4,5-T	Muranyi-Kovacs et al, 245	Mouse (C3Hf)	F	100 mg/l drinking water for 2 mon then 80 ppm in diet	Various	P<0.01
	NCI, Bionetics, 4	Mouse (B6C3F1, B6AKF1)	M,F	diet, sc injection	"	
Thiorurea	Fitzhugh and Nelson, 246	Rat (Albino)		100,250,500, 1,000 ppm/diet	Hepatic cell adenoma	
	Rosin and Rachmilewitz, 247	"	M,F	3,4,4 ml 10% solution 3x/wk im for 6 mon, then 0.2% solution in drinking water	Squamous-cell carcinoma, mixed-cell sarcoma	
	Gargus et al, 248	Mouse (ICR Swiss)		2,500 mg/kg single injection	Negative	
	Rosin and Unger, 249	Rat (Hebrew University)	M	0.2%/26 mon in drinking water	Myxomatous tumor of nose, epidermoid carcinomas of ear duct and orbit	

TABLE XIV-9 (CONTINUED)

EXAMPLES OF PESTICIDES CONSIDERED BY NIOSH TO REQUIRE FURTHER CARCINOGENICITY TESTING

Pesticide	Author, Ref	Species (Strain)	Sex	Dose and Route	Cancer Site	Statistical Significance
Trichlorfon	Gibel et al, 224	Rat (Wistar)	M,F	15 mg/kg/2x/wk oral	Spleen, various	
		"	M,F	15 mg/kg/2x/wk im	"	
		Mouse (AB)	M,F	Topical	Leukosis	
2,4,6-trichloro-phenol	NCI, Bionetics, 4	Mouse (B6C3F1, B6AKF1)	M,F	100 mg/kg/d, 21 d oral, then 260 ppm/ diet	Reticulum cell, liver	P=0.05

TABLE XIV-10

RESULTS OF MUTAGENICITY STUDIES WITH PESTICIDES

Pesticide	Test System*														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
DDT		-	-	-	+		-	-							
Methyl parathion	+	+	+	+											
Dimethoate	+	+	+	+											
Dichlorvos (DDVP)	+	+	+	+		-	-	-							
Oxydemeton-methyl	+	+	+	+	+										
Monocrotophos	+	+	+	+											
Pentachlorophenol		-	-	+	-	+	-								
1,2-Dibromoethane		+	+	+	+	-	+								
Captan		+	+	+	-		+	+							
Folpet		+	+	+	-										
Ethylene dibromide									+	+	+				
Ethylene oxide			+		+				+	+		+	+	+	
Ethylene chlorohydrin											+	+			+
1,2-Dibromo-3-chloropropane											+				
Dicrotophos	+			+											

1 = liquid holding test, forward mutations to 5-MT resistance in E coli
2 = spot test, back mutation in S marcescens and forward mutations in E coli
3 = liquid holding test, foward mutation to streptomycin resistance in E coli
4 = liquid holding test, mitotic gene conversion in S cerevisiae
5 = recessive lethal mutations in D melanogaster
6 = chromosome aberrations in human lymphocytes in vitro;
7 = host-mediated assay, back mutation in S typhimurium and S marcescens;
8 = dominant lethal test with mice;
9 = N crassa
10 = Tradescantia
11 = S typhimurium (TA 1530)
12 = S typhimurium (TA 1535)
13 = barley
14 = Drosophila
15 = K pneumoniae

Adapted from references 257-261, 234

TABLE XIV-11

PESTICIDES DISPLAYING NO SIGNIFICANT CARCINOGENICITY IN ASSAYS WITH EXPERIMENTAL ANIMALS

Anthraquinone	Methyl chloroform
Antu	Methyl selenac
Atrazine	Methyl zimate
Bismate	Monochloroacetic acid
2-sec-Butyl-4,6-dinitrophenol	Mucochloric acid
Butyl zimate	Nabam
alpha-Chloralose	1-Naphthalene acetamide
Cumate	1-Napthalene acetic acid
Dehydroacetic acid	1-Naphthyl-N-methyl carbamate
2,6-Dichloro-4-nitroaniline	Nickel dibutyl dithiocarbamate
alpha-(2,3-Dichlorophenoxy)-propionic acid	Noruron
alpha-(2,5-Dichlorophenoxy)-propionic acid	1,3,4,5,6,7,8,8-Octachloro-3a,4,7,7a-hexahydro-4,7-methano phthalen
2,4-Dichlorophenyl benzenesulfonate	Ovex
Dichlorvos	Pentachlorophenol
Dicryl	Phenothiazine
4-Dimethylamino-3,5-xylenol	Phenylmercuric acetate
Dimethyldithiocarbamic acid-dimethylammonium salt	Picloram
Diuron	Propazine
Dodine	Propyl ethylbutylthiocarbamate
2-(2,4-DP)	Rotenone
Ethyl cadmate	Simazine
Folpet	Sulfads
Gibberellic acid	Tetradifon
Indole-3-acetic acid	Thiram
Isolan	2,2'-Thiobis(4,6-dichlorophenol)
Ledate	2,2'-Thiobis(4,6-dichlorophenol), disodium salt
Malathion	2,4,6-Trichlorophenol
Maleic hydrazide	2-(2,4,5-Trichlorophenoxy)-propionic acid
Maneb	Unads
Methoxychlor	

Adapted from references 4, 250-254

TABLE XIV-12

COMPOUNDS REVIEWED BY NIOSH WHICH HAVE BEEN TESTED FOR TERATOGENICITY

Compound	Investigator's Conclusion	"Teratogenic" Effect Dose (mg/kg)	Number and Days of Doses Administered	Number of Animals Per Treated Dose (Animal/ Route)	Incidence of Terata/ Number of Fetuses: Control Group	Incidence of Terata/ Number of Fetuses: Treated Group	Fetal Abnormalities	Ref
Parathion	All three slightly teratogenic	3.5	1,d 11	5 (rat/ip)	0/43*	1/28	Edema	262
Diclorovos		15.0		4 "	0/33*	3/41	Omphalocelic	
Diazinon		200		4 "	0/25*	1/6	Hydrocephalic	
					0/25*	1/6	Phalanx missing	
					0/25	1/6	Ectromelic-	
		100		5 "	0/26*	6/50	dilated renal Pelvis	
Trichlorfon	Teratogenic	80	1,d 9 or 13	11 (rat/oral) "	-	-	General edema	263
Phosmet	"	30	1,d 9	9 "	-	-	Hypognathia Limb dislocation	
		30	1,d 13	8 "	-	-	Exencephaly Non-closing eyelid	
Aldrin	Teratogenic	50	1,d 7,8,9	41 (hamster/ oral)	1/55*	24/272*	Cleft palate	264
					0/155	20/272*	Cleft lip	
					0/155	1/272*	Fused rib	
Dieldrin	"	30	1,d 7,8,9	43 "	1/155	39/230*	Cleft palate	
					0/155	1/230*	"	
Endrin	"	5	1,d 7,8,9	39 "	1/155	16/148*	"	
					0/155	2/148	Cleft lip	
					0/155	10/148*	Fused rib	

TABLE XIV-12 (CONTINUED)

COMPOUNDS REVIEWED BY NIOSH WHICH HAVE BEEN TESTED FOR TERATOGENICITY

Compound	Investigator's Conclusion	"Teratogenic" Effect Dose (mg/kg)	Number and Days of Doses Administered	Number of Animals Per Treated Dose (Animal/ Route)	Incidence of Terata/ Number of Fetuses: Control Group	Incidence of Terata/ Number of Fetuses: Treated Group	Fetal Abnormalities	Ref
Aldrin	Teratogenic	25	1,d 9	10 (mouse/ oral)	0/70*	2/68*	Cleft palate	264
Dieldrin		15	1,d 9	"	0/70*	13/80*	Cleft palate	
Endrin		2.5	1,d 9	10 "	0/70*	5/82*	Cleft palate	
Captan		1,000	1,d 7,8	6 (hamster/ oral)		8/35	Exencephaly; cranial pimple; cleft palate	267
		750	1,d 6-10 or 6-8	5 "	7/1536	10/73	Exencephaly; cranial pimple; fused ribs	
		600		1 "		4/52	Fused ribs; limb defects	
		500		5 "		5/109	Exencephaly; fused ribs; cranial pimple; limb defects;	
				5 "			curved tail tail	
		300		5 "		9/11	Exencephaly; fused ribs	

TABLE XIV-12 (CONTINUED)

COMPOUNDS REVIEWED BY NIOSH WHICH HAVE BEEN TESTED FOR TERATOGENICITY

Compound	Investigator's Conclusion	"Teratogenic" Effect Dose (mg/kg)	Number and Days of Doses Administered	Number of Animals Per Treated Dose (Animal/ Route)	Incidence of Terata/ Number of Fetuses: Control Group	Treated Group	Fetal Abnormalities	Ref
Thiram (in DMSO)	Teratogenic	250 250	1,d 7 1,d 8	3 (hamster/ oral)	0/1053 3/1083 1/1083 2/1083 0/1083	1/16 1/16 4/6 1/6 1/16	Cranial nipple Shortened mandible/maxilla Fused ribs Limb defect Umbilical hernia	265
Thiram (in CMC)	"	250 250	1,7 1,8	11 (hamster/ oral)	0/1083 3/1083 1/1083 1/1083 0/1083	1/79 4/79 4/79 6/79 7/79	Cranial nipple Shortened maxilla/mandible Fused ribs Short/curved tail Umbilical hernia	
Diquat	-	7	1,d 6-14	-- (rat/ip)	--	--	Retarded sternum and oxicle growth	266
Paraquat	-	6.5	1,d 6	-- "	--	--	Cartilage malformations	

*Calculated figure

TABLE XIV-12 (CONTINUED)

COMPOUNDS REVIEWED BY NIOSH WHICH HAVE BEEN TESTED FOR TERATOGENICITY

Compound	Investigator's Conclusion	"Teratogenic" Effect Dose (mg/kg)	Number and Days of Doses Administered	Number of Animals Per Treated Dose (Animal/ Route)	Incidence of Terata/ Number of Fetuses: Control Group	Incidence of Terata/ Number of Fetuses: Treated Group	Fetal Abnormalities	Ref
Folpet	-	1,000	1,d 7,8	1 (Hamster/ oral)		3/7	Fused rib; short/curved tail	267
		900	1,d 6-10 or 6-8	3 "		5/25	Exencephaly; fused rib; cranial pimple	
		800		3 "		1/66	Limb defect	
		700		6 "	7/1536	2/56	Short/curved tail; fused rib	
		600		9 "		8/74	Exencephaly; fused rib; limb defect	
		500		10 "		3/91	Exencephaly; limb defect; cleft palate; short tail	
Captafol	-	500	1,d 8	13 "		15/132	Exencephaly; cranial pimple	267
		400	1,d 6-10 or 6-8	8 "	7/1536	14/61	Exencephaly; fused ribs; short tail	
		300		6 "		1/63	Limb defect	
		200		15 "		4/145	Cleft palate; umbilical hernia; short/curved tail	
2,4,5-T	Teratogenic	300	1,d 12,13	20 (mouse/ oral)	6/995	39/340	Cleft palate	267

TABLE XIV-12 (CONTINUED)

COMPOUNDS REVIEWED BY NIOSH WHICH HAVE BEEN TESTED FOR TERATOGENICITY

Compound	Investigator's Conclusion	"Teratogenic" Effect Dose (mg/kg)	Number and Days of Doses Administered	Number of Animals Per Treated Dose (Animal/ Route)	Incidence of Terata/ Number of Fetuses		Fetal Abnormalities	Ref
					Control Group	Treated Group		
2,4,5-T	Teratogenic	113	1,d 6-14	18 (mouse/ sc)	41/4176*	174/79*	Cleft palate	269
+ DMSO	"		d 6-15	14 "	4/496	27/97*	"	
+ Dioxin	"	113	d 9-17	10 "	0/106*	20/36*	"	
2,4,5-T	"	113	1,d 6-14	12 (mouse/ oral)	0/227*	13/58*	"	
+ Dioxin	"	113	d 6-15	7 "	0/106*	20/37*	"	
2,4,5-T	"	113	1,d 6-14	12 (mouse/ oral)	0/227*	13/58*	"	
+ Dioxin		113	d 6-15	7 "	0/106*	20/37*	"	
2,4,5-T	"	46.4	1,d 10-15	6 (rats/ oral)	0/122*	0/16*	No cleft palate	
+ Dioxin	"							
2,4,5-T + 2.9 ppm Dioxin	"	100	1,d 6-10	6 (hamster/ oral)	0/975	4/77	Eye abnormalities; cleft palate; ectopic heart	270
2,4,5-T, no detectible Dioxin	"	100	1,d 6-10	8 "	0/975	7/38	Delayed head ossification; limb deformity	

TABLE XIV-13

EXAMPLES OF ADVERSE REPRODUCTIVE EFFECTS DUE TO PESTICIDES

Pesticide	Species	Dose/Concentration	Effect	Ref
Kepone	Mouse	5-37.5 ppm/diet	Decreased size and number of litters	271
	"	10-37.5 ppm/diet	Decreased size, number and survival of liters	
Mirex	Rat	0.2-50 mg/injected once	LH inhibition and cecreased ovulation	273
Aldrin	Dog	0.15-03 mg/kg/d, oral	Delayed estrus, inability to mate, decreased mammary development, frequent still-births, low offspring survival	274, 275
Aldrin & p,p'-DDT	"	0.15 mg/kg aldrin plus 6 mg/kg p,p'DDT/d, oral	Delayed estrus, decreased mammary development, frequent stillbirths, low offspring survival	274, 275
p,p'DDT	"	12 mg/kg/d, oral	Delayed estrus, inability to mate, decreased mammary development, frequent still-births, low offspring survival	274, 275
Technical DDT	Mouse	12.5-50 mg/kg, oral	Reduced testosterone uptake by prostate	276
Dieldrin	"	1.25-5 mg/kg, oral	"	276
2,4,5-T	"	6.25-25 mg/kg, oral	"	276
Carbaryl	Rat	14 mg/kg/d, diet	Estrus prolonged, sperm motility reduced, disturbed spermatogenesis, ovary disturbances	277
Heptachlor	"	6 mg/kg/diet	Decreased litter size, increased perinatal litter mortality	278
Crufomate	"	Dipped, 2 d before or 10 d after mating	Decreased number of litters	279

TABLE XIV-14

ORGANOPHOSPHORUS INSECTICIDES SUSPECTED OF DELAYED NEUROTOXICITY
BASED ON EXPERIMENTAL EVIDENCE IN CHICKENS

Compound	Dose, Route	Ref
Haloxon	3 x 200 mg/kg, oral	285
EPN*	40 mg/kg, sc	287
	60 mg/kg, sc	286
	40 mg/kg, sc	99
DEF	7 x 100 mg/kg, ip	288
	200 mg/kg, sc	99
Merphos	10 x 100 mg/kg, ip	288
	600 mg/kg, sc	99
Carbophenothion*	640 mg/kg, sc	99
	2 x 500 mg/kg, sc	**
DMPA	50 mg/kg, ip	289

*Not delayed but irreversible
**MK Johnson, written communication, May 1978

TABLE XIV-15

GENERAL CLASSIFICATION OF TOXIC MATERIALS

LD50 (oral administration) Values	Toxicity Designation
<5 mg/kg	Super toxic
>5 to 50 mg/kg	Extremely toxic
>50 to 500 mg/kg	Very toxic
>500 to 5,000 mg/kg	Moderately toxic
>5,000 to 15,000 mg/kg	Slightly toxic
>15,000 mg/kg	Practically nontoxic

Adapted from reference 333

TABLE XIV-16

EPA CLASSIFICATION

Hazard Indicators	Toxicity Categories			
	I	II	III	IV
Oral LD50	Up to and including 50 mg/kg	From 50 thru 500 mg/kg	From 500 thru 5,000 mg/kg	>5,000 mg/kg
Inhalation LC50	Up to and including .2 mg/l	From .2 thru 2 mg/l	From 2 thru 20 mg/l	>20 mg/l
Dermal LD50	Up to and including 200 mg/kg	From 200 thru 2,000	From 2,000 thru 20,000	>20,000
Eye effects	Corrosive;corneal opacity not reversible within 7 d	Corneal opacity reversible within 7 d; irritation persisting for 7 d	No corneal opacity; irritation reversible within 7 d	No irritation
Skin effects	Corrosive	Severe irritation at 72 hr	Moderate irritation at 72 hr	Mild or slight irritation at 72 hr

Adapted from 40 CFR 162

TABLE XIV-17

DOT CLASSIFICATION CRITERIA FOR CLASS A AND B POISONS

	Dose	Species	Observation Period
LD50 (oral) mg/kg	50	White rat	48 hr
LC50 (inhalation) mg/l	2	"	48 hr
LD50 (dermal) mg/kg	200	Rabbit	24 hr

Adapted from 49 CFR 173.343

TABLE XIV-18

CLASSIFICATION PROPOSED TO WHO, 1972

Class I
(a) Oral LD50 (rat) <200 mg/kg;
OR
(b) Formulation containing any concentration of an active ingredient with oral LD50 (rat) ≤25 mg/kg.
Class II
Not in Class I(a) and 200 mg/kg ≤ oral LD50 (rat) ≤2,000 mg/kg
Class III
Not in Class I(a) and 2000 mg/kg ≤ oral LD50 (rat) ≤5,000 mg/kg
Class IV
Oral LD50 (rat) > 5000 mg/kg but no active ingredient with oral LD50 (rat) ≤200 mg/kg

Adapted from reference 336

LD50 (rat) mg/kg	Extremely Hazardous
Oral	
Solids	≤ 5
Liquids	≤20
Dermal	
Solids	≤10
Liquids	≤40

Adapted from reference 337

TABLE XIV-19

CLASSIFICATION, 1975

Highly Hazardous	Moderately Hazardous	Slightly Hazardous
5-50	50-500	> 500
20-200	200-2,000	>2,000
10-100	100-1,000	>1,000
40-400	400-4,000	>4,000

TABLE XIV-20

RUSSIAN CLASSIFICATION

	I Extremely Toxic	II Highly Toxic	III Moderately Toxic	IV Slightly Toxic
LD50 (oral) mg/kg	<15	15-150	<151-1,500	>1,500
LC50 (inhalation) mg/l	<.5	.5-5	< 5-50	> 50
LD50 (dermal) mg/kg	<100	100-500	<500-2,500	>2,500

Adapted from reference 338

TABLE XIV-21

BULGARIAN CLASSIFICATION

	Extremely Hazardous	Very Hazardous	Moderately Hazardous	Slightly Hazardous
LD50 (rat) oral mg	< 50	0-100	100-1,000	>1,000
LD50 (rat) dermal mg/kg	<100	0-500	500-2,000	2,000
Inhalation toxicity LC50 for rat 4 hrs exposure	<200 mg/m^3. The concentration of saturation is higher or equal to the toxic one; provokes heavy acute poisonings	<100 mg/m^3. The concentration of saturation is higher than the threshold one; provokes poisonings	1,000-5,000 mg/m^3. The concentration of saturation causes slight effect and is about the threshold one	>5,000 mg/m^3. The concentration of saturation provokes no effect
Elasterogenic effect	Proved cancerogenic (sic) for people. Strong cancerogens (sic) for test animals	Slight cancerogenic (sic) for test animals. Effect in less than 20% of the animals with max. untoxic doses. Suspected carcerogen (sic)	No cancerogenic (sic) effect	No cancerogenic (sic) effect
Teratogenic effect	Proved or suspected teratogenecity (sic) in humans, reproducible in exp. animals. Teratogenic activity at levels similar to that of human exposure	Strong teratogens: affect more than 50% of the offsprings at doses not toxic to the mother. Politropic adverse effects. Active in several animal species	Proved teratogenecity (sic) for one species only, affects single or single organ or system, effective dose above 1/10 LD50	No teratogenecity (sic)
Embryotoxicity	Is not recorded in the assessment	Selective embryotoxicity. Manifests with doses not toxic for the mother	Moderate embryotoxicity. Manifests with doses toxic for the mother	No embryotoxic effect

Adapted from reference 337

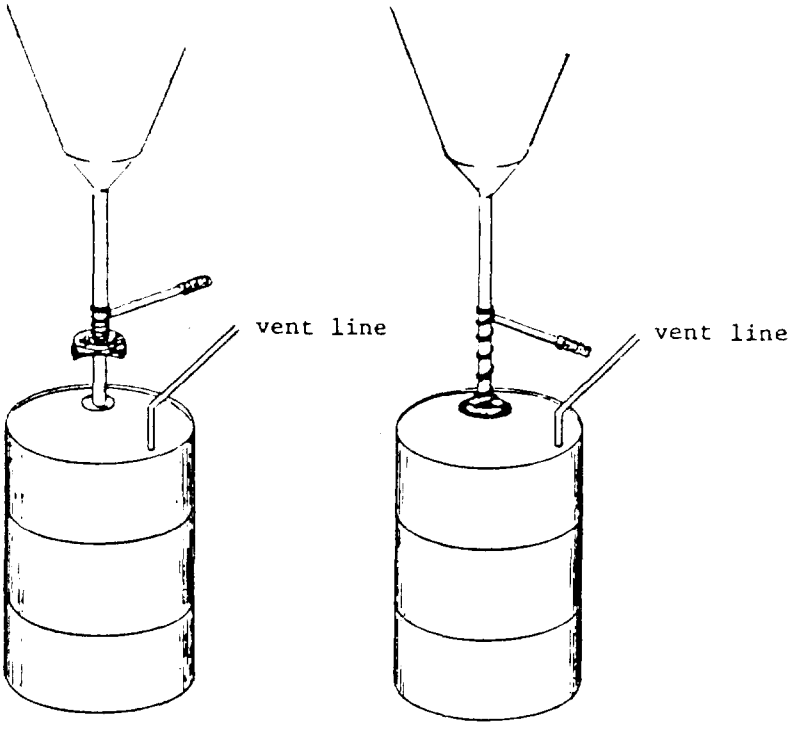
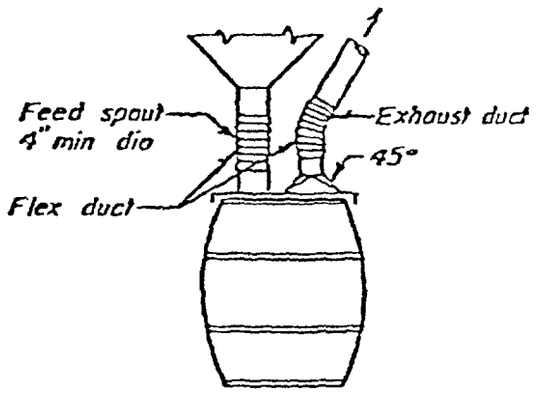


FIGURE XIV-1

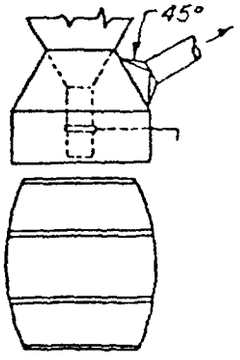
SPRING-LOADED RUBBER COLLAR AND VENT LINE FOR DRUM FILLING



Adapted from reference 343

FIGURE XIV-2

EXAMPLE OF LOCAL EXHAUST SYSTEM FOR DRUM AND BARREL FILLING



Adapted from reference 343

FIGURE XIV-3

EXAMPLE OF LOCAL EXHAUST SYSTEM FOR DRUM AND BARREL FILLING

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